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ENVIRONMENTAL IMPLICATIONS OF GENETIC ENGINEERING

HEARING

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT

AND THE

SUBCOMMITTEE ON
SCIENCE, RESEARCH AND TECHNOLOGY

OF THE

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SCIENCE AND TECHNOLOGY
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ENVIRONMENTAL IMPLICATIONS OF GENETIC ENGINEERING

WEDNESDAY, JUNE 22, 1983

House of Representatives,
Committee on Science and Technology,
Subcommittee on Investigations and Oversight,
Subcommittee on Science, Research and Technology,
Washington, D.C.

The subcommittees met, pursuant to notice, at 9:37 a.m., in room 2325, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the Subcommittee on Investigations and Oversight) and Hon. Doug Walgren (chairman of the Subcommittee on Science, Research and Technology) presiding.

Present: Representatives Gore, Walgren, Brown, MacKay, Volkmer, Skeen, Schneider, McCandless, and Sensenbrenner.

Mr. **Gore**. The subcommittees will come to order.

I would like to welcome all of our witnesses and guests today. We hope to have an interesting and useful hearing on the environmental implications of genetic engineering.

In the late 1860's, a French astronomer named Leopold Trouvelot brought into this country a few eggs of a relatively obscure variety of European moth. Living at the time in Medford, Mass., Trouvelot kept these eggs and the moths that hatched from them at his home, as he tried in vain to breed a new, disease-resistant form of silk worm. As luck would have it, a few of Trouvelot's prized creatures escaped.

From this insignificant beginning, the gypsy moth ranks today as one of the most disastrous environmental pests in this Nation's history. In 1981 alone, gypsy moths defoliated over 10 million acres of trees around the country.

The tale of the gypsy moth is instructive, for it provides many lessons about the potential that exists for large-scale environmental damage from very small beginnings. It is not an isolated example. Like dutch elm disease, chestnut blight, and countless other examples, including kudzu in my native Tennessee—and if there are any southerners in the audience, you know what kudzu is—like all of these examples, the gypsy moth illustrates the problems that can occur when new foreign organisms are introduced into our environment.

In the mid-1970's, as recombinant DNA technology became widely utilized in laboratory experiments, great public concern arose over the possibility that some deadly new virus, or chemical kudzu, might escape from a lab and endanger surrounding populations. In response to this concern, guidelines for experiments were developed, and today genetic engineering experiments are carried out with relative safety in the labs. Indeed, we can all share the luxury of assuming that those early concerns were overblown.

As concern over threats to public health have subsided, however, a new set of concerns about genetic engineering has developed. These concerns entail not human health, but the safety of the environment. They emanate out of a fear not so much that an organism will escape, but that its deliberate release will produce serious ecological consequences.

Over the last several years, the commercial applications of biotechnology in both industry and agriculture have blossomed tremendously. In agriculture, new varieties of genetically engineered plants are being created, and new genetically engineered pesticides are being manufactured. In industry, microbes are being developed to break down toxic waste, clean up oil spills, produce new forms of energy, and perform countless other tasks. We have even seen the creation of "super mice," announced last December, in experiments aimed at improving animal husbandry.

One of my constituents asked me why we wanted to make mice twice as large as normal mice and speculated as to whether the surplus cheese problem might have something to do with that. [Laughter.]

All of these developments unquestionably have great potential benefits for our society. But the commercial success of these applications of biotechnology will ultimately depend upon their ability to be introduced into the environment on a widespread basis.

Already steps are being taken to introduce new organisms into the environment. The National Institutes of Health Recombinant DNA Advisory Committee has approved field tests for three new genetically engineered plants, and undoubtedly many more requests for field tests will soon be forthcoming.

Soon there will be efforts to conduct field tests of microbes as well. It is the increasing likelihood of such deliberate releases on a broader scale—as biotechnology moves out of the laboratory and into the environment—that causes concern over environmental impacts.

The organisms that are being created today through genetic engineering are far more exotic than any creatures that have existed before. These are organisms with completely new genotypes, and, consequently, their potential for environmental damage could be far greater than for any "natural" organism. It is important, therefore, that we understand all the potential environmental ramifications of an organism before it is released into an ecosystem—instead of waiting and finding out about them after the damage has occurred.

At the same time, however, as we consider the issues raised by the introduction of these organisms into the environment, we have to be careful not to unduly inhibit their development. Our society has much to gain from these uses of biotechnology. It is simply the case that we can benefit even more from the commercial applications of biotechnology if we utilize them in an environmentally safe manner.

The purpose of this hearing today is to consider how we do just that. We will examine the environmental implications of the new technology and the question of environmental impacts. We will examine the potential benefits to be reaped from the technology and consider how we should balance these benefits against any environmental risks that may exist. And we shall consider what role the Federal Government should play in all of this.

I would like to call upon my cochairman, Hon. Doug Walgren.

Mr. **Walgren**. Thank you, Mr. Chairman.

It is with real interest that the Subcommittee on Science, Research and Technology joins in these hearings with the Oversight and Investigations Subcommittee of the Science and Technology Committee. These are areas that are of very broad interest to Members of Congress, and particularly the members of these two subcommittees.

As you know, molecular biology, recombinant DNA technology, and all the other areas that are generally considered in the field of genetic engineering are some of the most exciting research areas in science today. There has been literally an outpouring of technical papers, presentations, and conferences that exemplify the activity in this field. The promise and the potential of genetic engineering have attracted some of the finest minds in science and, as a result, discoveries and breakthroughs and the progress that is being made is occurring at a pace that no one would have anticipated only several years ago.

As a result, both the benefits and the problems that once seemed quite far into the future are rushing on us and truly are with us now. The development of new or modified plant species, of microbes which degrade pollutants, methods to enhance oil or mineral resources, larger or faster growing animals with higher yields of meat or milk—these are all applications of genetic engineering which are occurring or will occur in the near future. As such, these developments have the potential of providing tremendous social and economic benefits to our society. However, we must make sure that in reaching for these benefits we do not inadvertently do damage, what may be irreparable damage, to parts of our environment.

The purpose of our hearing is threefold. We will hear of past experience with the introduction of new organisms into the environment. We will learn something about the current research that might result in the introduction of new genotypes into the environment and the possible effects of that activity. Finally, we will explore how we best insure, how we presently insure, and how we ought to think about insuring through the legislative and regulatory processes, the application of genetic research in an environmentally responsible way.

I certainly want to express my appreciation to the cochairman of the hearing for the work that he and his committee have done on this. We want to join in that effort in hope that we can develop a broad-based record and a wider interest and exposure to Members of Congress to the facts of this area.

Thank you, Mr. Chairman.

Mr. **Gore**. Thank you.

Should legislation become obvious and necessary, we will, of course, look forward to working together on that as well.

I would like now to call on the ranking minority member of the Investigations Subcommittee, Joe Skeen.

Mr. SKEEN. Thank you, Mr. Chairman. I thank both of the chairmen of these two subcommittees.

The prospect of having kudzu in grits is intriguing. [Laughter.]

There are few issues before this subcommittee that hold such diametric potential: An opportunity for immeasurable good, while at the same time carrying the possibility for incalculable harm. Genetic engineering research, of course, is directed to solve major world problems in the fields of medicine, agriculture, and nutrition, and other areas. The overwhelming impact of this research will benefit mankind for the rest of all time. The periodic news accounts we read of new breakthroughs will become more and more numerous until they become the bulk of scientific progress. The possibilities for good are endless.

But genetic engineering is complex, as you all know, and there is an unprecedented potential for environmental harm, since mistakes affect not only our lifetime, but remain forever, passing on to the future evolution of the directly affected organisms and perhaps those associating with them. We rarely get philosophical in this body, but when we realize that man has unlocked the secrets of evolution itself, a reason for pause is established.

I say this because I don't want anyone to think that we have not considered all these possibilities. The oversight history of this committee is proof of our longstanding concern.

We meet today because we are impressed with recent developments in this field. I am more pleased than concerned, frankly, especially with the developments in agriculture. While it looks like we won't see the benefits of current research until the next decade, everyone in the agricultural community will applaud the work. Plant growth regulation, biocontrol of pests, self-fertilization, and herbicide and climatological resistance all serve vastly to improve our major food crops.

New Mexico State University, in my district, has developed quite an expertise in the application of biotechnology to agriculture. Their work in biochemical, microbial, and somatic cell genetics and stress physiology holds great promise for semiarid agricultural crops in New Mexico and around the world.

I am anxious to hear today's distinguished witnesses, and I want to welcome you all today.

Thank you, Mr. Chairman.

Mr. GORE. Thank you.

Let me call our first panel of witnesses to the witness table. We have three panels, incidentally. The first one is on environmental and regulatory issues: Dr. Martin Alexander from the Department of Agronomy at Cornell; Dr. Fran Sharples, my fellow Tennessean—and a special welcome to you, Dr. Sharples—from Oak Ridge National Laboratory in Oak Ridge, Tenn.; and Dr. Geoff Karny—Mr. Geoff Karny, I'm sorry, who speaks with such authority on these issues that we sometimes inadvertently give him a title that he doesn't have—a legal analyst with the Office of Technology Assessment here in Washington, who has helped us on many of these related issues in the past.

We will have three panels today. After the witnesses have testified, we will hold questions until the end of each panel to ask the panel as a group.

Without objection, the prepared statements of each of these witnesses will be put into the record in full. If you care to summarize any portions of your statements, please feel free to do so.

Dr. Alexander, we would like to begin with you. We are honored to have you here and look forward to your testimony.

STATEMENT OF DR. MARTIN ALEXANDER, DEPARTMENT OF AGRONOMY, CORNELL UNIVERSITY, ITHACA, N.Y.

Dr. **Alexander**. Thank you, Mr. Chairman.

At the outset, I should state my belief that genetic engineering will greatly benefit mankind. I feel that we are at the start of a period when major changes will occur in agriculture, industry, and technologies to maintain environmental quality as a result of the creation of new and novel genotypes.

On the other hand, the history of the introduction of technologies has much to teach us. In many instances, the risks of these technologies were not initially evident, but they became quite clear as the technology became widespread. Often, the harmful effect occurred at very low frequency, but the impact was quite large. Antibiotics, for example, revolutionized our approach to chemotherapy, but a significant number of people suffered severe and often irreversible damages from the use of the wonder drugs. DDT prevented an enormous amount of human misery, but the harmful effect of this insecticide became evident with time. The industrial revolution provided materials which would never have been available otherwise, but it was the prelude to air pollution.

The proponents of these technologies, and many others that could be cited, minimized or ignored the risks in the past or still do so. The lure of major benefits from these technologies has been so great that their proponents have been unwilling to consider the possible undesirable consequences.

With regard to the possible environmental consequences arising from the release of new genetic materials, I, for one, do not know whether there will or will not be an undesirable effect, but I believe we can assess the probability of a detrimental influence on humans, other species, or the function of natural environments.

It is possible to distinguish five components of risk associated with the release of organisms with new genotypes. Each component has a probability of occurring ranging from zero to 100 percent. These factors are: first, the chance of release into a natural environment—and I refer to not only the deliberate release but the inadvertent release through existing types of programs; second, the possibility that the organism will survive in that environment; third, the likelihood that it will grow there; fourth, the possibility that it will make contact with a species that it can injure; and, fifth, the chance that it will be harmful.

If the new life form is deliberately released to perform some useful environmental function, and it does what is expected of it, only the last two factors need to be considered; that is, will it make contact with a species which it can harm and will it then bring about the deleterious change.

It is sometimes argued that new genotypes will not survive or grow because genetic changes of ecological benefit have already occurred and exist in nature. This is one of the main arguments in the past. All other genetic changes, according to this argument, including those that may be created in the laboratory, will be ecologically disadvantageous, and organisms bearing these changes will have no survival or growth capability in nature. This argument is wholly unconvincing because we are now able to bring about multiple genetic changes in sequence, and we do this in the laboratory. One species is modified to give a new genotype; that genotype is modified once again to give a third type; and the third variety is modified once again to give still a new type. In this way, we may be able to create new genotypes from organisms that would not have survived in nature, and the new life form may have survival and growth capabilities that its genetic precursors would not possess.

Some individuals argue that the containment facilities in laboratories working with new genotypes will prevent the inadvertent discharge of any harmful organism. This is the first risk factor. However, even with highly trained individuals and with a very few excellent containment facilities that exist, inadvertent releases of disease-producing organisms have occurred in this country. If these releases have taken place in the best of our facilities and with highly trained individuals, one can speculate what might occur with individuals who are not well trained, with individuals who do not take the environmental issues seriously, with no monitoring or effective regulation of their actions, and with facilities that are far from the best.

It is also argued that organisms introduced in environments in which they are not indigenous will not survive. This is the second risk factor. This view is completely contrary to the enormous body of information. The scientific literature contains numerous examples showing that many microorganisms are able to survive days, weeks, months, and even years, although these species were not present in the environment before their deliberate introduction.

The third risk factor. It is also argued that an introduced organism will not grow in an environment in which it is not native. This, too, is contrary to the existing body of information. Admittedly, few species multiply in environments in which they were initially alien. However, examples are easily found of species that have proliferated even though they were not present in that habitat before.

Let me emphasize that a small percentage of the individual microorganisms in the enormous populations that we work with in the laboratory and in industry will likely escape. Some will, however. Most of the species that are released into waters and soils will not survive, but a few will. Most of those species which survive in natural environments will probably not multiply. However, some will. Thus, the probability associated with each of these risk factors cannot be deemed to be zero. It may be very small, but it is not zero.

Furthermore, differing from chemicals, air pollutants, and radiation, microorganisms are able to increase in abundance. We get an expanding base of pollution. The problem of detrimental effects, if it does exist, is magnified simply because living organisms reproduce, often at extremely rapid rates.

I should say that I come from an area which, as of 2 years ago, never sprayed for gypsy moth. We are now spraying, and it is now moving west.

We also have on our lawns another introduced species of plant which we did not have before, and it, too, is spreading.

It is frequently stated that the slight changes arising from genetic engineering will not alter the harmfulness of organisms. However, this view also does not conform with what we know about the behavior of microorganisms. The slight genetic changes, admittedly induced or noted in the era before genetic engineering, do bring about major modification in the potential harmfulness of some microorganisms. One example, probably the best known, is the change in resistance to antibiotics that appeared with time among disease-producing microorganisms. Thus, we lose control of pathogens by antibiotics which were once very effective against them. Another example is the genetic variant of the influenza virus that appeared in 1918, killing millions of people. This was a natural genetic change that had an enormous impact in many, many countries and in some areas wiped out 25 percent of the human population.

It is difficult to see why a manmade genetic change would necessarily behave any differently from those occurring spontaneously in nature. It, too, could proliferate. It, too, could spread. It, too, could do harm.

Disasters arising from introduced microorganisms are also well known. A single microbial species eliminated most chestnuts from 50 million acres of the United States. In the 1970's, a fungus spread rapidly through the corn crop of the United States, reducing the yield by 10 percent, not an insignificant amount in terms of dollar income for farmers who were growing corn.

The microroganism causing smallpox killed more than 95 percent of the native Indians of Mexico. Hence, if a microorganism has the capacity to survive and grow and if it makes contact with an appropriate host, these several risk factors, it may spread rapidly to the host population and cause disastrous changes.

It is, thus, my view that alien organisms that are inadvertently or deliberately introduced into natural environments may survive, they may grow, they may find a susceptible host or other environment, and they may do harm. The probability of all these events occurring is small, but the consequences of this low probability event may be enormous.

Although genetically engineered species have not been subjected to all the risk factors I have cited, we have never made meaningful tests of the probabilities of any of these risks. Therefore, it seems foolhardy to make dogmatic statements as to whether there will or will not be a detrimental effect. The prudent course of action is to establish the risk factors and simultaneously develop a regulatory procedure to assess survival, growth, and deleterious effects. In this way, we may gain the benefits of genetic engineering while not being exposed to the likely hazards from the misuse of the technology.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Alexander follows:]

PRESENTATION TO: SUBCOMMITTEES ON SCIENCE, RESEARCH AND TECHNOLOGY AND ON INVESTIGATIONS AND OVERSIGHT

Martin Alexander

Cornell University, Ithaca, New York 14853

Recent years have seen considerable discussion and controversy about the benefits and hazards of genetic engineering. Unfortunately, much of the discussion has resulted in a polarization of positions, and eminent biologists have frequently expressed views that are not based on knowledge of the environmental sciences. It is surprising to listen to or read these discussions and see how little science there is to support such very strong views. Some of these individuals, who are unquestionably highly competent in their own disciplines, believe that the probability of there being an undesirable ecological effect is absolutely zero, whereas others feel that the likelihood is almost 100 percent. During the period I served as chairman of the Recombinant DNA Study Group of the EPA Science Advisory Board, I was surprised to hear or read strong statements expressed with a minimum of scientific evidence or convincing reasoning. Since these discussions of the Science Advisory Board of EPA, no significant information has been gathered and no substantive research program has been initiated to establish or argue against the likelihood of some ecological or biological hazard arising from the deliberate or inadvertent introduction into waters and soils of new life forms.

At the outset, I should state my belief that genetic engineering will greatly benefit mankind. I feel that we are at the start of a period when major changes will occur in agriculture, industry, and technologies to maintain environmental quality as a result of the creation of new and novel genotypes. In agriculture, new varieties of plants will be introduced, and we shall see vaccines and other products to enhance beef and milk production. Industries concerned with chemical manufacturing, pharmaceuticals and food products will also benefit greatly from these developments. I am also convinced that we shall see new organisms and biotechnologies to destroy pollutants that are otherwise only slowly destroyed by biological mechanisms.

On the other hand, the history of the introduction of technologies has much to teach us. In many instances, the risks of these technologies were not initially evident, but they became quite clear as the technology became widespread. Often, the risk occurred at a very low frequency, but the impact was quite large. Radiation therapy was a boon to medicine early in this century, but its use resulted in radiation sickness. Antibiotics revolutionized our approach to chemotherapy, but a not insignificant number of people suffered severe and often irreversible consequences from the use of the wonder drugs. DDT prevented an enormous amount of human misery and widespread mortality resulting from insect vectors of human, animal and crop diseases, but the harmful effect of this insecticide became evident with time. The industrial revolution improved our standard of living and provided materials which would never have been available otherwise, but it was the prelude to air pollution. Atomic energy offers enormous promise where fuels for energy production are in short supply, but many people feel that the dangers are quite substantial. The proponents of these technologies, and many others that could be cited, minimized or ignored the risks in the past or still do so. The lure of major benefits from these new technologies has been so great that their proponents have been unwilling to consider the possible undesirable consequences. Few, if any, major technologies have been introduced without some untoward effect.

With regard to the possible ecological consequences arising from the inadvertent or deliberate release of new genetic materials into waters and soils, I for one do not know whether there will or will not be an undesirable effect, but I believe we can assess the probability of a detrimental influence on humans, other species or the function of natural environments.

It is possible to distinguish five components of risk associated with the release of organisms with new and novel genotypes. Each component has a probability of occurring ranging from zero to one hundred percent. These risk components are: (1) the chance of release into a natural environment, (2) the possibility that the organism will survive there, (3) the likelihood that it will grow in that environment, (4) the possibility that it will make contact with species that it can injure, and (5) the chance that it will be harmful. If the new life form is deliberately released to perform some useful environmental function, and it does what is expected of it, only the last two factors need to be considered; that is, will it make contact with a species that it can harm and will it bring about that deleterious change.

It is sometimes argued that new genotypes that are inadvertently released will not survive or grow because genetic changes of ecological benefit have already occurred and exist in natural ecosystems. All other genetic changes, including those that may be created in the laboratory, will be ecological disadvantageous, and organisms bearing these changes will have no survival or growth capability in terrestrial or aquatic environments. This argument is unconvincing because we are now able to bring about multiple genetic changes in sequence: one species is modified to give a new genotype, that genotype is modified once again to give a third type, and the third variety is modified once again to give a fourth, etc. In this way, we may be able to create new genotypes in the laboratory from organisms that would not have survived in nature, and the highly modified, new life form may have survival and growth capabilities that none of its genetic precursors would possess.

Some individuals argue that the containment facilities in laboratories working with new genotypes will prevent the inadvertent discharge of any harmful organism. In this country and abroad, there are facilities which have excellent containment, and these laboratories are staffed with individuals who have spent years in acquiring skills to prevent release of the harmful organisms with which they work. However, even with these highly trained individuals and with presumably excellent containment facilities, inadvertent releases of disease-producing organisms have occurred. In this country, for example, at both the Center for Disease Control and the Plum Island facility, where work is done with highly contagious organisms, occasional accidents and consequent discharges have taken place. If these releases have taken place in the best of our facilities and with highly trained individuals, one can only speculate what might occur with individuals who are not well trained in containing potentially hazardous organisms, with individuals who do not take the issues seriously, with no monitoring or effective regulation of their actions, and with facilities that are far from the best.

It is also argued that organisms introduced into environments in which they they are not indigenous will not survive. This view is completely contrary to an enormous body of scientific information. Although most species that are introduced into alien environments do in fact die out, the scientific literature contains numerous examples, some of which come from our studies, showing that many microorganisms are able to survive days, weeks, months, and even years although these species were not present in the environment before their deliberate introduction.

It is also argued that an introduced organism will not grow in an environment in which it is not native. This too is contrary to the existing body of scientific information. Admittedly, few species multiply in environments in which they were initially alien. however, examples are easily found of species that have proliferated even though they were not present in that habitat before. For example, farmers in the midwest and elsewhere regularly introduce a microorganism into soil that causes nitrogen fixation after it infects soybean roots. This microorganism was not previously present in many of these soils, but after it was deliberately introduced, it was able to survive and it did indeed proliferate. Moreover, it has a major effect on plant growth, but fortunately in this instance, the effect is highly beneficial.

Let me emphasize that a small percentage of the individual microorganisms in the enormous populations worked with in the laboratory and in industry will likely escape. Some will, however. Most of the species that are released into waters and soils will not survive, but a few will. Most of those species which survive in natural environments will probably not multiply; however, some will. Thus, the probability associated with each of these risk factors cannot be deemed to be zero. It may be very small, but it is not zero.

Furthermore, differing from chemicals, air pollutants, and radiation, microorganisms are able to increase in abundance. The problem of detrimental effects, if it does exist, is magnified simply because living organisms reproduce, often at very rapid rates. Other types of environmental stresses tend to be dissipated with time, but the potential harm from living organisms may spread and become increasingly severe.

It is frequently stated that the slight changes arising from genetic engineering will not alter the harmfulness of organisms. However, this view also does not conform with what we know about the behavior of microorganisms. Slight genetic changes, admittedly induced in the era before genetic engineering, do bring about major modifications in the potential harmfulness of some microorganisms. The changes that modify the antigenicity of the influenza virus become evident in the low immunity in humans exposed to the virus; such people may develop influenza. Slight modifications in the metabolism of disease-producing microorganisms make them resistant to the drugs used for their control, so that antibiotics and other chemotherapeutic agents are no longer effective. The slight genetic changes that result in a capsule structure to be formed around certain bacteria make them resistant to the defense mechanisms of humans and animals.

We have no history of the effects of genotypes created by man. However, much is known about deleterious effects of new genotypes that have arisen spontaneously. Such new organisms become prominent because they possess some selective advantage. Thus, the use of antibiotics has allowed for the widespread occurrence of new genotypes of the organisms causing gonorrhea and staphylococcal infections. The use of fungicides in agriculture has allowed new genotypes of plant pathogens to proliferate and have harmful effects on major crops. Similarly, the influenza virus presumably undergoes regular genetic changes in nature, and these genetic changes lead to the widespread dissemination of the virus, frequently with an enormous number of human deaths; here, the selective advantage of the new genotype is not obvious. It is difficult to see why a man-made genetic change would necessarily behave any differently from those occurring spontaneously in nature: it too could proliferate, spread, and do harm to susceptible humans, animals, plants, or microorganisms important to natural environmental functions.

Disasters arising from introduced microorganisms are well known to epidemiologists, animal scientists, and plant pathologists. The microorganism causing the Dutch elm disease in a few years nearly wiped out the population of susceptible trees. A single microbial species is estimated to have eliminated most chestnuts from 50,000,000 acres of the United States in but a few years. In the 1970s, a fungus spread rapidly through the corn crop of the United States, and the disease induced is estimated to have reduced the corn yield in this country by 10 percent, clearly a major impact. A virus deliberately introduced into Australia nearly wiped out the rabbit population of that country. Influenza affects many humans each year, but when a new genetic variant of the influenza virus appeared in 1918, millions of people were killed. It has also been estimated that the microorganism causing smallpox killed more than 95 percent of the native indians of Mexico, and that about 90 percent of the natives of Hawaii died because of the introduction of new microorganisms into the islands. In most but not all such instances, the microorganisms did not represent new genotypes, but rather they were existing organisms that moved to a new environment. The reason I cite these well known epidemiological facts is to illustrate that a microorganism that has the capacity to survive and grow, if it makes contact with an appropriate host, may spread rapidly through the host population and cause disastrous changes.

It is thus my view that alien organisms that are inadvertently or deliberately introduced into natural environments may survive, they may grow, they may find a susceptible host or other environment, and they may do harm. I believe that the probability of all these events occurring is small, but I feel that it is likely that the consequences of this low-probability event may be enormous.

The arguments presented are based on a series of separate but known cases in which one type of organism escapes from a containment facility, another survives, a third is able to grow, and a fourth finds a host and causes an affect. We have no illustrations of genetically engineered species which have been subjected to all these risk factors. Nevertheless, we have never made meaningful tests of the probabilities of these newly created genotypes and even have little information on existing organisms. Therefore, it seems foolhardy to make dogmatic statements as to whether there will or will not be a detrimental effect. The prudent course of action is to establish the risk factors and simultaneously develop a regulatory procedure to assess survival, growth, and deleterious effects. Assessments of potential survival and growth can be done at modest cost. Procedures do not now exist to measure deleterious effects of microorganisms on natural populations at low cost, but there has not been a significant amount of research to develop such procedures. In this way, we may gain the many benefits of genetic engineering while not being exposed to the likely hazards from the misuse of the technology.

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M.S., Bacteriology, University of Wisconsin, 1953
B.S., With highest honors, Rutgers University, 1951

Employment: 1955-present - Assistant, Associate, Professor, and now Liberty Hyde Bailey Professor, Cornell University. Member, Department of Agronomy. Joint appointment, Section of Ecology and Systematics, Division of Biological Sciences. Member, graduate fields of Microbiology, Soil Science, Ecology, and Toxicology. Adjunct Distinguished Scientist, Boyce Thompson Institute for Plant Research.

Awards and Honors:

Fisher Award for Applied and Environmental Microbiology, American Society for Microbiology, 1980.
Distinguished Visitor Award, Board of Foreign Scholarships, 1977.
Fellow, Soil Science Society of America, 1976.
Fellow, American Academy of Microbiology.
Industrial Research-100 Award, 1968.
Fellow, American Association for the Advancement of Science, 1967.
Fellow, American Society of Agronomy, 1967.
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Books: INTRODUCTION TO SOIL MICROBIOLOGY, 1977
MICROBIAL ECOLOGY, 1971
ADVANCES IN MICROBIAL ECOLOGY, Volume 1 through 5 (Editor), 1977 through 1981.

More than 325 technical papers and reviews in microbiology, environmental pollution, and soil and aquatic sciences.

Mr. GORE. Thank you very much. It is an interesting statement. We will hold questions until the other two panelists have completed their testimony.

Dr. Fran Sharples from Oak Ridge National Laboratory, a special welcome to you. We are delighted to see you here.

Please proceed with your testimony.

STATEMENT OF DR. FRANCES E. SHARPLES, OAK RIDGE NATIONAL LABORATORY, OAK RIDGE, TENN.

Dr. SHARPLES. Thank you very much for the opportunity to come and talk to you about this work that I have done.

I would like to explain for a moment how I got involved with the subject of novel genotypes. Two years ago I was awarded an environmental science and engineering fellowship by the U.S. Environmental Protection Agency. The environmental science and engineering fellowships are designed to get scientists from the academic and outside community into the Government to act as special research consultants to work in EPA and assist the Agency in identifying and assessing the significance of long-range environmental problems. The particular problem I was asked to work on as an ecologist was assessing the probability that a novel organism produced by genetic engineering could become established in the environment and cause damage. Since no releases, either accidental or deliberate, of such organisms were known to have occurred, it was necessary to deal with the question by looking at the analogy of introduced organisms, exotic species.

The importation and release of exotic organisms is a phenomenon which is very familiar to ecologists. Dr. Alexander has just been talking about it. What I hoped to be able to do was to survey the ecological literature and try to get a handle on what percentage of the cases of exotic introduction actually result in ecological dislocations or disruptions.

The introduction of exotic organisms, although there are natural mechanisms by which this phenomenon occurs, the number of cases that have been due to human activity are far and away the larger share. Thousands of plants, mammals, fish, and birds have been imported from one environment to another for uses such as the provision of food, game species, hunting, fishing, and ornamental uses. I might add that a lot of these importations have been not only beneficial, but essential. For example, almost every one of our major crop species is an introduced plant. There are almost no native agricultural crops in North America.

Unfortunately, there have also been accidental transports of rodents, insect pests, and pathogens to every continent and remote islands just about all the way around the globe. Wherever there have been lanes of commerce, the numbers of organisms that have been transported by man in ships, airplanes, whatever form of transportation you can think of, have been very large.

Charles Elton, who was one of the founding fathers of ecology, estimated that the number of species that have spread from their native homes to new environments is probably in the tens of thousands and perhaps even in the hundreds of thousands. In spite of the fact that we have documentation of many, many cases of the phenomenon, we do not really know what the total number is.

We do know that those which become established are only a fraction of the total number that are introduced, and those which cause problems, as Dr. Alexander said, are a still smaller fraction.

When there is a dislocation, however, it can be quite significant. In the natural environment of an organism there are a multiplicity of natural control factors, such as predators, parasites, pathogens, competitors, or perhaps a limited food supply, which act to keep the numbers of the population of an organism at reasonable levels, in balance with its environment.

When an exotic is transported into a new environment, in most cases or many cases these control factors, natural control factors, are not present. Therefore, if an exotic manages to become established, it can undergo ecological explosion and increase enormously in number. In the process it can displace native organisms, it can prey on them or cause disease, and in so doing destroy them.

Eventually, exotic explosions tend to subside as new control mechanisms become established and a new organism becomes integrated into its new environment. But the point is that even if an exotic does eventually become integrated, the environment it has penetrated is different afterward, and may contain fewer species, and it may be a simpler environment. Simpler is correlated with its being more vulnerable to perhaps another exotic invasion.

The problem is that unless an exotic causes a dramatic effect, though, we may not even really know that it is there. For example, it has been mentioned a couple of times that the chestnut blight and the dutch elm disease caused, and are still causing in the case of the elm, very noticeable disappearance and mortality in some of our major tree species, but other microscopic organisms that are not pathogenic may be present in the environment and not be detected for long periods of time. If there is no dramatic effect, we may not even realize that they are there, and whether they are causing damage is hard to say.

We know that this type of phenomenon has happened in the past because, for example, in the rhizobium strains that are common in our soybeans, the nitrogen-fixing bacteria that live with our soybeans, we can detect the presence of a strain which is identical or very similar to one which is a dominant strain in China. The inference can be made that at some point the bacterium was brought here from China and it has been doing very well in our environment, probably since around the turn of the century. It probably has not caused a problem.

Another problem with the ecological literature that is available is that in most cases we do not have records of cases where introductions have failed. However, in some cases there are records. For example, in the 19th century there was a craze—it amounted to a craze—to introduce the European bird species to this continent to provide European immigrants with the birds that they were familiar with from their homelands. There were dozens of species of birds introduced, and only two that we know about very well from that particular period of social activity became established. Those were the starling and the house sparrow. Interestingly enough, the habits of both of those birds—the fact that they were destructive agricultural pests—was well established before these animals were brought over here. Therefore, it probably would not be unfair to say that that level of planning in the past, that level of looking at what the possible consequences of introducing an exotic would be, was typical in the old days.

Mr. GORE. Dr. Sharples, in Tennessee we are kind of hoping that somebody will invent a new microbe that can eat starlings. [Laughter.]

Dr. SHARPLES. And kudzu, too.

Mr. GORE. And kudzu.

Dr. SHARPLES. Furthermore, there is no systematic way to understand which of the multiplicity of factors—and I mentioned some of them before—contributes to the success or failure of an exotic in a new environment. In fact, similar situations can have drastically different outcomes. There is a case that was related in a paper by the ecologist Robert Paine where in two lakes, one in Guatemala and one in Uganda, an effort was made to upgrade the local fishery by introducing large species of predatory fish. In the lake in Guatemala the fish in question was the striped bass. The outcome was that the bass essentially destroyed the native fishery, caused a fish-eating bird which was endemic to that area to become an endangered species essentially, and caused the native fishery that produced income for the local people to become inviable.

In a similar situation, a similar lake in Uganda, a large sport fish was introduced, the Nile perch, against the advice of biologists who said for a long period of time, 25 years, that meddling with a complex ecosystem was not a good idea. Anyway, the fisheries people went ahead and introduced the fish, and it is doing beautifully. It has provided a tourist attraction. It produces something like three times as much protein for the local people as the native fishery, which is unharmed, did. It worked out beautifully. The reason that the two situations had such drastically different results is simply not clear. We just do not understand them.

The consensus, then, from looking at the ecological literature, is that the outcome of an introduction is not predictable. Rather, most ecologists refer to what can happen with an introduced species as a gamble, a game of chance, biological roulette. The chance is both that there will be high risk or the risk of a drastically terrible outcome is high, but also there is a chance that the rewards, if the operation is successful, will be high.

I would like to emphasize that the terms "unpredictable" and "hazardous" are not necessarily synonymous.

What we do know about exotic species is, qualitatively that the outcome of an exotic introduction depends on both the nature of the organism that is doing the invading and the nature of the environment that is being invaded.

Vulnerable environments, environments which are particularly likely to have a problem, are those which are isolated, for example, remote island systems like Hawaii; or simplified, like agricultural systems where the number of organisms in the system in total is very limited; or, last, environments which are disturbed or stressed, such as polluted aquatic ecosystems.

What makes a good exotic? A good exotic in general could be said to be an organism which is flexible, which is opportunistic, which has high reproductive capability, good dispersal capability, and is generally able to take advantage of whatever resources are at hand. It also helps that most exotic organisms don't arrive with their own predators or pathogens.

I would just like to summarize what I have said. The literature on exotic introductions reveals that foreign species do not invariably produce adverse ecological changes. Ecologists believe that only a fraction of immigrating species actually produces ecological dislocation while the majority probably fail to penetrate existing biotic assemblages. Unfortunately, there is no a priori way to know whether a particular introduced organism will or will not cause disturbances purely on the basis of what we know from historical events.

Efforts directed at devising a quantitative probability for the establishment and disruption by a novel organism based on the number of negative results that have already occurred would not be meaningful for a number of reasons.

First, what constitutes a negative result is not always clear and may be a matter of interpretation.

Second, very little attention is ever paid to exotic organisms unless they become a problem, but we simply do not know how many introduced organisms have failed to get a foothold and disappeared.

Third, ecologists usually do not understand enough about the complex interactions in an ecosystem to be able to predict the outcome with any degree of certainty. There are too many uncontrolled and unknown factors at this point to handle new situations on anything other than a case-by-case basis. There are currently no economically and technically feasible ways to screen large numbers of new organisms to determine if they will have an adverse ecological effect if released into the huge variety of available environments.

It is possible to design microorganisms which are not able to survive outside a laboratory or industrial setting, but if the point of releasing an organism to clean up a pollutant spill is that it has to survive for a week or a month, designing an organism so that it will self-destruct in the environment is obviously self-defeating. Therefore, if it is deemed that it is desirable for these organisms to survive in the environment, then the appropriate thing, I think, to do is to start doing some research that develops some form of valid testing on what the effects of such introductions might be.

That is all. Thank you.

[The prepared statement of Dr. Sharples follows:]

TESTIMONY BEFORE THE SUBCOMMITTEES ON
SCIENCE, RESEARCH AND TECHNOLOGY
AND
INVESTIGATIONS AND OVERSIGHT
OF THE
COMMITTEE ON SCIENCE AND TECHNOLOGY,
U.S. HOUSE OF REPRESENTATIVES

HEARING ON ENVIRONMENTAL IMPLICATIONS OF GENETIC ENGINEERING

JUNE 22, 1983

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I wish to express my sincere appreciation for the opportunity to testify at this hearing today. Before I begin my technical discussion, I think that it is important to explain to you how I came to be involved with the subject of novel genotypes.

My formal academic training was in vertebrate ecology, and I hold both master's and doctoral degrees in zoology from the University of California at Davis. In 1981, I was awarded an Environmental Science and Engineering Fellowship by the U.S. Environmental Protection Agency (EPA). The selection process for this fellowship program is managed by the American Association for the Advancement of Science in a manner very similar to that of the Congressional Science and Engineering Fellowship Program with which some of you may be familiar. Environmental Science and Engineering Fellows work as special research consultants within EPA to assist the agency in identifying and assessing the significance of long-range environmental problems. The particular long-range problem I was asked to work on was assessing the probability that a "novel" organism produced by genetic engineering could become established in the environment and cause ecological damage.

Since no releases of such organisms, either deliberate or accidental, were known to have occurred, it was necessary to address the issue by relying on an analogous situation with which ecologists are very familiar, i.e., the introduction of "exotic" or non-native organisms into new environments. The importation and release of exotic plants and animals has occurred often and sometimes with dramatic results. Any of the Subcommittee members who have seen roadsides covered in kudzu or trees defoliated by gypsy moths have witnessed the kinds of results I am referring to. What I was really interested in finding out, however, was whether it is possible to say what proportion of past exotic introductions have become serious problems. This would be an essential first step in formulating a probability of risk for a man-made novel organism causing damage. Therefore, I delved into as much of the ecological literature on exotic introductions as I could in the ten-week period of my Fellowship.

To further complicate matters, it is possible to argue that the analogy between exotic organisms and man-made novel genotypes is not really valid. It is possible that a genetically engineered organism with less than 1% new genes is not qualitatively the same as a "totally new" exotic organism introduced into an ecosystem from another continent or hemisphere. I felt it was necessary to formulate some judgements about the validity of the analogy. To do this, I looked at some of the recent literature on the development of pesticide resistance in insects and antibiotic resistance in microorganisms. Resistance may be defined as a decreased response on the part of an organism to a control agent as a result of application of that control agent. Development of resistance is a dynamic adaptive reaction at the genetic level to intense, though unintentional, selection by man. This selection results in a proliferation of organisms with new combinations of genes that were probably exceedingly rare under natural conditions. These "new" organisms are no longer affected by the chemical and can eventually replace non-resistant forms. Once this replacement occurs, the pest is again free to undergo a population explosion and become even more out of balance with its ecological surroundings. Such imbalances can have great medical and economic significance. It seemed reasonable to try to get a sense of what magnitude of genetic change is correlated with the development of these results by investigating what is known about the genetics of resistance.

The complete results of this study are available in my final report which is titled "Spread of Organisms with Novel Genotypes· Thoughts from an Ecological Perspective." It was first published as an Oak Ridge National Laboratory Technical Manuscript in October 1982. It is about to be republished in the Recombinant DNA Technical Bulletin which is produced by the Office of Recombinant DNA Activities of the National Institutes of Health. If there are no objections, I would like to submit a copy of this report for the record, since there will not be time to do more than summarize its conclusions in the remainder of my oral presentation. I should emphasize that these conclusions are based on my own opinions only, that they do not necessarily reflect the views of EPA, and that no official endorsement of these views should be inferred.

Introduction of Exotic Species

Although there are natural mechanisms by which plants, animals, and microorganisms disperse from their native environments to new ones, by far the largest share of exotic introductions is due to human activity. Wherever man has traveled, he has transported a huge variety of other organisms with him. Thousands of species of plants, mammals, birds, and fish have been transplanted deliberately for food, sport, or ornamental uses. Rodents, insect pests, or disease-causing microorganisms have been transported accidently to every continent and to remote islands, often in spite of heavy quarantine. Wherever there have been lanes of commerce, these have furnished pathways for invasions of foreign organisms.

In spite of the fact that the ecological literature documents hundreds of cases of exotic introduction, no one really knows how many species have spread from their native homes. Charles Elton, one of the founding fathers of ecology, estimated that the total number of introductions that have occurred world-wide must be in the tens of thousands. The number of organisms that have become established and have managed to persist in their new homes is certainly only a fraction of the total, but this fraction could still amount to thousands of species. The number of introduced organisms that not only become established but also actually produce ecological disruptions is a still smaller fraction. Nevertheless, the small proportion of cases which result in ecological dislocation can be very significant indeed. In their native environments, organisms are usually subject to a whole variety of forces which have the effect, in sum, of causing the size of a population to stay within reasonable limits. Predators, parasites, pathogens, competing species, or a limited food supply may work separately, or in concert, to regulate the size of a population of organisms. When transported to a new environment where none of these natural control mechanisms may be present, an exotic organism may, as Elton put it, undergo an ecological explosion, increasing enormously in number. In the process, the exotic may exclude or destroy native organisms by usurping a food supply, causing disease, or preying upon them. Over the long term, an exotic organism may finally become integrated into a system it has successfully penetrated. This integration is usually marked by a major reduction in number of individuals from outbreak proportions to more moderate levels. In the meanwhile, however, the penetrated environment may have become simpler, may contain fewer native species, and is certainly, in the end, different from what it was in the pre-invaded state.

The problem is that unless an exotic organism does become a problem, we may not even realize that it is, or was, there in our environment. One reason for this is obvious if we consider that some of the organisms in question are microscopic. The virtual demise of the American chestnut and the dead or dying elm trees here on the streets of Washington bear witness to the introduction of two lethal fungi known as "chesnut blight" and "Dutch elm disease." These two organisms are respectively believed to have arrived here accidentally on nursery plants from Asia and in infected timber used for veneers. But how many non-pathogenic microorganisms have successfully taken up residence here unnoticed, we will probably never know. There is evidence that the event happens at least occasionally. A microbiologist at the Department of Agriculture's Beltsville experimental station reported to me, for example, that one of the most common and successful strains of the beneficial nitrogen-fixing bacterium infecting soybeans here in the United States is the same type as the dominant strain in China. The inference drawn was that this bacterium was probably introduced here in soil or plant material early in this century and has been holding its own in competition with our native strains ever since.

At any rate, we do not have any accurate idea of how many organisms have been introduced and have simply failed to become established. In a few rare instances, records of deliberate attempts at introduction which failed are available. For example, in the 19th century, it became a popular craze to try to transplant European bird species to the United States. This "Acclimatization" movement apparently started with European immigrants in America who missed seeing and hearing the birds that were familiar to them. Dozens of species of birds were imported from Europe and released here, but only two of these introductions were successfully established. Regrettably, these two were the house sparrow and the starling. Interestingly enough, the fact that both birds were destructive agricultural pests was already known long before their introduction here. It is probably not terribly unfair to say that this marked lack of foresight is rather typical of many past attempts to introduce exotics.

In most cases, however, introductions which fail go unrecorded. Consequently, it is difficult, if not impossible, to devise meaningful quantitative estimates of the probability of any organism persisting in a new environment based on what is currently known from the ecological literature. Furthermore, there is no systematic understanding of which of the multiplicity of natural factors contribute to the success or failure of an exotic species in a new environment. In fact, the introduction of two similar exotics to two similar but far removed ecosystems may have drastically different results. For example, the ecologists Robert Paine and Thomas Zaret related the following illustration. Efforts to upgrade the local fisheries of two lakes, one in Guatemala and one in Uganda, were made in this century. Both efforts consisted of the deliberate introduction of large predatory fish (the large-mouth bass in Guatemala, and the Nile perch in Uganda) which were supposed to provide an additional food source for the local peoples and stimulate the tourist industry. In Guatemala, the bass grew rapidly at the expense of the smaller native fish which were severely reduced in number. The populations of a native crab were also depleted, and a native fish-eating bird became seriously threatened. At the time their article was written (1975), Paine and Zaret reported that the bird required protection, the native fishery and the income it once provided had been destroyed, and the bass could only be caught with scuba or electric fishing techniques which were beyond the means of local fishermen. Meanwhile, the Nile perch was transplanted to the lake in Uganda despite 25 years of advice from biologists against the action on the basis that the risks of meddling with a complex ecosystem were not worth the potential benefits. The introduction appears, however, to have been a rousing success. Long-term average catch figures for native fish (12,000 tons/yr) seemed to be unaffected, an additional 34,000 tons of perch were being caught annually, and the perch fishery had, in fact, become an important and successful tourist attraction. The biological reasons for the failure of one effort and the success of the other are unclear. The consensus amongst ecologists is that the outcome of an introduction is, in most instances, not predictable. Rather, the introduction of an exotic organism is viewed as a game of chance, a gamble, with the possibility of both high risks and high rewards.

What is understood about exotic introductions is that the outcome is determined by both the nature of the invaded environment and the nature of the invading organism. Environments that are particularly vulnerable to successful invasion are those that are isolated (e.g., remote islands), simplified (e.g., agricultural systems), or stressed and disturbed (e.g., polluted). As for what makes a successful exotic, the most important requirements would seem to be that it not be overly specialized, that it have high reproductive and dispersal capabilities, and that it be a good or aggressive competitor. All of these factors are generally related to an ability to be opportunistic and take advantage of whatever resources are available. The gypsy moth can, for example, feed on 450 to 500 different plant species and shows great behavioral flexibility in accommodating to adverse conditions. It also helps that most exotics make their appearance unaccompanied by their own predators or parasites and frequently enter environments with no defenses specifically tailored to work against the invader.

In summary, the changes brought about by the introduction of a foreign organism can vary from nearly unnoticeable to dramatic and unmistakable. Competition between exotics and natives can result in the reduction or exclusion of native forms, as can predation, parasitism, or pathogenicity on the part of the invader. The stress placed on a system by a foreign species may also contribute to the establishment of other exotics to cause further unbalance. Over the long term, however, a new organism may finally become integrated into the system it has penetrated. This integration is usually marked by a major reduction in number of individuals. The reasons for the decline of exotics, when this occurs, are just as obscure as the reasons for their explosive spread in the first place. Two things must, however, be kept in mind. The more disturbed, artificial, or simplified an environment is, the less likely it is that a new balance can be struck in a reasonable time. Second, even if an exotic becomes integrated, the system it entered has been modified and is different and perhaps simpler. The desirability of creating such new systems will, in many cases, remain a matter of debate.

Finally, I would like to touch very briefly on what I learned about the development of resistance to chemical controls. The development of pesticide resistance in insects has become an increasingly serious matter as chemical after chemical is rendered ineffective. The medical, economic, and ecological implications are large. Our ability to control insect-borne diseases and to retain agricultural productivity can be greatly impaired as a result of the genetic changes we unintentionally induce in insect pest species. It is interesting to note that although the biochemical mechanisms of resistance in insects are diverse, they have time and time again turned out to be due to monofactorial (single-gene) changes. In the case of DDT-resistance, for example, at least three different mechanisms are known, each of which is controlled by a single gene. In concert, the three produce resistance intensities that are multiplicative rather than additive. The point that I am trying to make is that very small changes in an organism's genetic information can produce large changes in its function in the environment and in turn have an extremely large impact on its economic status.

Similarly, the genetic modifications which result in antibiotic resistance in bacteria are small. They are frequently also associated with the extranuclear genetic material known as plasmids. Plasmids are often the vehicles by which new genes are "engineered" into bacteria. Many bacteria seem to be able to readily transmit plasmid-borne genes to other bacterial species. The ease with which new genes can be inserted into a bacterium via a plasmid vector in the laboratory may thus be a two-edged sword. It may be very difficult to keep inserted genes isolated in single bacterial strains. While I am an ecologist and not a geneticist, I am reasonably confident that this observation warrants looking into further.

In any case, I believe that the likelihood of an organism becoming established and persisting in a given environment is an ecological question regardless of the origin or nature of the differences that make such an organism "exotic" or "novel." The proportion of the genome which is "new" is not necessarily correlated with the degree of impact an organism can have on an ecological system. I believe that the analogy between recombinant organisms and introduced species is a valid one.

The literature on exotic introductions reveals that foreign species do not invariably produce adverse ecological changes. Ecologists believe that only a fraction of immigrating species actually produces ecological dislocation while the majority probably fail to penetrate existing biotic assemblages. Unfortunately, there is no a priori way to know whether a particular introduced organism will or will not cause disturbances purely on the basis of historical evidence. Efforts directed at devising a quantitative probability for establishment and disruption based on the number of negative results that have already occurred would not be meaningful or fruitful for a number of reasons. First, what constitutes a negative result is not always clear and may be a matter of interpretation. Second, very little attention is ever paid to exotic organisms unless they become a problem, but we do not really know how many have been introduced and failed to get a foothold. Third, ecologists usually do not understand enough about the complex interactions in an ecosystem to be able to predict the outcome of an introduction. There are too many uncontrolled and unknown factors at this point to handle new situations on anything other than a case-by-case basis. There are currently no economically and technically feasible ways to screen large numbers of new organisms to determine if they will have an adverse ecological effect if released into the huge variety of available environments. It is possible to design microorganisms which are not able to survive outside a laboratory or industrial setting; but if the purpose for which such an organism is engineered requires that it survive in the environment long enough to do its job, such a design might be self-defeating. If it is desirable for engineered organisms to survive in the environment, then research to develop some form of valid test on what effects their introduction might have would be very much in order.

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"Environmental Regulation and Legislation". New York University Seminar, August 14 and 15, 1978, New York City.

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Research Associate, Program Planning and Analysis Office, ORNL, 1982 - Present. Manager of the Laboratory's Institutional Planning activities.

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Teaching Assistant, University of California, Davis, Department of Zoology, 1972-1975, 1976-78.

Teaching Assistant, Barnard College, Department of Biology, 1969-70, 1971-72.

Mr. GORE. Thank you very much. That was very good testimony.

Without objection, I would like to include in the record your report entitled "Spread of Organisms with Novel Genotypes, Thoughts from an Ecological Perspective." I am informed by staff that this report is soon to be published in an NIH recombinant DNA technical bulletin.

[See Appendix A.]

Our final witness on this panel is Geoffrey Karny, legal analyst with the Office of Technology Assessment.

Mr. Karny, welcome. Please proceed.

STATEMENT OF GEOFFREY M. KARNY, SENIOR ANALYST, BIOLOGICAL APPLICATIONS PROGRAM, OFFICE OF TECHNOLOGY ASSESSMENT, CONGRESS OF THE UNITED STATES

Mr. KARNY. Thank you, Mr. Chairman.

I am pleased to appear here on behalf of OTA to present our views on the regulatory situation with respect to the release of genetically modified organisms into the environment.

Current regulation of recombinant DNA processes and products consists of a combination of: First, the quasi-regulatory NIH guidelines; second, Federal laws designed to protect human health and the environment; and, third, State and local health and environmental laws, including tort law. This regulatory system is generally viewed as adequate to address any risks presented by recombinant DNA with the possible exception of the deliberate release of genetically modified organisms into the environment.

I would like to address the remainder of my remarks to the case of deliberate release.

You have heard two other experts provide quite detailed information about the risks involved. I would just like to add one or two other points on that, to address the question of why we should be concerned about deliberate release.

First, the techniques involved are vastly more sophisticated and powerful than the crude ones we have used in the past, and there is much we do not know about the organisms being created. In addition, deliberate release would appear to present different risks from the other uses of organisms that contain recombinant DNA. First, there is the obvious but crucial difference that the organisms are not contained. I would like to point that out which is quite well known, anyway, but I would just make the point that the NIH guidelines are based on the concept of containment. Therefore, we really have a question of their relevance here.

The second point is the one we have talked about before, about the novel organisms being introduced and examples of the problems caused.

As to how applicable that prior experience is, I think it is interesting to point out two contrasting features. First, usually when organisms are changed in marked ways, as would be the case here, the organism becomes less competitive with indigenous or wild-type organisms. It is simply a matter of empirical experimentation that has shown that fact.

On the other hand, as was pointed out, for these organisms to survive in the environment for the types of uses that we might desire them to be used for, then they would have to be designed to be competitive with existing organisms. Again, there is that conflicting situation.

Given this limited information about risks, the question is: Is the regulatory structure adequate? To address that, I would like to outline the applicability of following parts of the regulatory environment: First of all, the NIH guidelines; second of all, the Federal environmental statutes, particularly TSCA; third, USDA-administered plant and animal pest control statutes, and I will just touch very briefly on those; fourth, relevant principles of tort law.

The NIH guidelines apply to all research involving recombinant DNA in the United States or its territories conducted at or sponsored by an institution receiving support for recombinant DNA research from NIH. The other Federal agencies that fund research have required their grantees to also follow the guidelines and, as far as we know, private companies are following the guidelines. Of course, the guidelines are not binding on the private sector.

The guidelines create an administrative framework that specifies the responsibilities of the parties involved. I want to mention just a few points on that.

First, the key organization on the institutional level is the Institutional Biosafety Committee. They oversee all the work with regard to recombinant DNA at the institution.

On the Federal level, the key people are the Director of NIH, who is the final decisionmaker under the guidelines, and the Recombinant DNA Advisory Committee, which is a diverse group of experts advising the Director in the major technical and policy issues involved.

Basically, the guidelines classify experiments into four categories ranging from exempt to those requiring RAC, which is the Recombinant DNA Advisory Committee, review and NIH and IBC approval prior to initiation. The deliberate release of such genetically modified organisms fall in that last category.

From a regulatory perspective, there are at least two potentially important limitations with regard to how the NIH guidelines deal with deliberate release. Whether these limitations are significant or not depends on one's view of the risk presented by deliberate release.

First, virtually all of the scientific experts on the RAC are molecular biologists or experts in human health. No one is an ecologist. There is some expertise with regard to plants, and it may be possible for RAC to overcome its limitations in this field of agricultural expertise by drawing on the USDA and EPA.

The second potential limitation lies in the RAC review procedure itself. Proposals to do the experiments are submitted to RAC members, who study the information submitted prior to their meetings. The requests range anywhere from one page to several pages with attached scientific articles, although the RAC can request additional information. Decisions are made after whatever study has been given prior to that RAC meeting.

I would just contrast that with the drug approval process or the pesticide approval process, where there is a major comprehensive, detailed review of drugs and pesticides before they are marketed.

Turning now to Federal environmental statutes, the most relevant ones are TSCA and FIFRA, which is the Federal Insecticide, Fungicide and Rodenticide Act.

TSCA authorizes EPA to acquire information on "chemical substances" in order to identify and evaluate the potential hazards and then to regulate the production, use, and distribution of those substances. The heart of TSCA is the premanufacturing notice requirement for new chemical substances in section 5. The point there is that TSCA is a notice statute. The burden is on EPA to regulate or prohibit the manufacture, sale, or disposal of those chemicals or to ask for additional information. This is, again, in contrast with certain other regulatory statutes such as FIFRA and the Federal Food, Drug, and Cosmetic Act, which put the burden on the manufacturer to prove safety before the product is released.

Now as far as the applicability of TSCA, it depends on definitions. A key definition is the definition of a chemical substance. I have laid it out there in the prepared statement.

Just to follow up on that, I think that definition would include recombinant DNA molecules. However, it is unclear, I think, whether the definition would encompass genetically modified organisms. One could argue, on the one hand, that the definition should encompass organisms because the language is quite broad, that Congress intended the definition to be broadly construed, and, finally, that Congress intended TSCA to fill the gaps in the other environmental laws.

On the other hand, the definition refers to "a particular molecular identity." I think it is arguable whether a living organism has a particular molecule identity. We just do not know everything that is in there, basically.

Now EPA itself has taken conflicting positions on the question of whether the term, "chemical substance" includes a living organism. I have laid out their statements on this in the prepared statement. Both statements, in fact, refer to congressional intent. It is an interesting point. I think the legislative history is ambiguous on this point.

EPA's Office of Toxic Substances, in a draft policy paper, has taken the position that TSCA would apply to those organisms. EPA itself has not taken any formal position, as far as I know.

Mr. Gore. What was the phrase in the patent law that the court interpreted—of course, we have Dr. Chakrabarty already here—in "Chakrabarty v. Diamond," the novel—do you remember the phrase?

Mr. Karny. With regard to what?

Mr. Gore. It seems to me a similar question was presented there as to whether or not a living——

Mr. Karny. Oh, I see, the question of subject matter patentability. Yes, it was a question of whether the organism was manufacture or composition of matter, and the court held really that the organism was a composition of matter or a manufacture.

I think that might be a little different going back to the——

Mr. Gore. Of course, it is very different in many ways, but the similarity is that a law designed for nonliving entities, or at least designed without realizing that living entities would come under its purview, was interpreted by the court to encompass it.

Mr. Karny. I think that is a good point to make. I would think the arguments are stronger for interpreting TSCA to cover living organisms. I personally think some very strong arguments could be made. The reason I am raising the question is that I think if somebody wanted to fight that interpretation through litigation or otherwise, I think they would have a case, maybe not a good case, but they would have a case.

I also think there is a consensus developing that TSCA should cover and would cover living organisms. If that interpretation were to be taken, TSCA would have good potential for regulating the deliberate release of genetically modified organisms.

Under section 4, EPA can adopt rules requiring the testing of chemical substances that may present an unreasonable risk of injury to health or the environment, and if other conditions are met.

Section 5 requires the manufacturer of a new chemical substance, presumably in this case a new organism to be released into the environment, to notify EPA 90 days before beginning production and submit any test data that it might have on that chemical's effects on the environment and on health, human health.

If EPA decides the data is insufficient to make the kinds of evaluations necessary, and if the substance may present an unreasonable risk or will be produced in substantial quantities, EPA can propose an order to restrict or prohibit the new chemical substance's manufacture or use.

Finally, under section 6, EPA can prohibit or regulate these substances if it finds that it presents or will present an unreasonable risk of injury.

TSCA also provides for certain recordkeeping and information gathering which would be important in this area.

However, despite this applicability, this theoretical applicability, there are other potential limitations to applying TSCA to this situation.

I should note a correction in the prepared statement. The prepared statement indicates that it is limited to microorganisms. I would like to change that.

Mr. Gore. What page are you on?

Mr. Karny. It is page 11 of the prepared statement.

Mr. Gore. Thank you.

Mr. Karny. I indicate that TSCA might be limited in terms of its ability to regulate genetically engineered microorganisms, and I would intend that not to be limited to microorganisms but to apply to any genetically engineered organism.

Moving on from that, as to these limitations, first of all, EPA has little expertise or experience with regard to genetic engineering. Second, its toxic substances program has been understaffed, according to a 1980 GAO study. Third, TSCA may not give EPA sufficient regulatory authority if the risks presented are viewed as substantial. For example, section 5 does not require the generation of toxicological data, nor general safety studies. Again, TSCA is primarily a notification statute. The burden is on EPA to take the legal action if it believes that insufficient data exists with regard to new chemical substances.

I want to briefly talk about FIFRA because it will also apply to this situation. FIFRA will cover genetically manipulated organisms that are used as pesticides. In the case of FIFRA, there is no uncertainty as to its applicability to those kinds of pesticides. Under FIFRA, EPA registers a pesticide; it is essentially a premarketing clearance procedure where EPA reviews data on safety and efficacy.

Now EPA has proposed a rule on data requirements for pesticides which also covers genetically manipulated ones. I think that is important to look at because that proposed rule sets extensive data requirements with regard to information that ought to be available to the agency before a biological pesticide is used in the environment. I think something is to be learned from looking at those data requirements.

Moving on briefly to the USDA plant and animal quarantine laws, I simply listed them in the prepared statement. I am not familiar enough with them to really do the analysis of their applicability. I think that is a question that is best addressed to the representatives from USDA.

Finally, I would like to just mention briefly the applicability of tort law because I see it as a quasi-regulatory tool with regard to this situation.

Basically, a tort is a civil wrong, other than a breach of contract, for which a court will award damages or other relief. Two well-known examples are medical malpractice and product liability cases.

I think it is important to remember tort law because it is a flexible, judge-made law applied on a case-by-case basis. If necessary, it is available to fill the gaps, if any, that are existing in the current regulatory structure, particularly with regard to deliberate release.

Although the tort law is designed primarily to compensate injury, the large dollar amounts that might be involved in such compensation would act as incentive for people who would release such organisms into the environment to do extensive testing as to their safety.

There are basically two points of tort law that would be applicable to this situation, or two concepts. One is the area of negligence, and the other is the area of strict liability, which includes the concept of product liability. In view of the time, I will not go into those other than to mention with regard to the concept of negligence that there is a concept called a standard of care against which a defendant's conduct is measured. In this situation, clearly, the guidelines would be one standard that a court would look at. But there are the limitations in the guidelines in terms of deliberate release because they simply state that organisms should not be released without the approval of NIH and IBC and upon the advice of RAC.

There may be a second standard which is more applicable, and that would be the information in proposed regulations I referred to previously under FIFRA. Part of those regulations with regard to the registration of pesticides set out the kinds of data requirements that a biological pesticide should have. That would seem to me to be very applicable to this situation.

In conclusion, I would like to state, first, that with the exception of FIFRA there is no Federal law that clearly covers the deliberate release of genetically modified organisms into the environment. TSCA has the potential to be applied, and the consensus seems to be developing that such organisms are included within the act's definition of chemical substance. Whether or not the courts would uphold such interpretation, of course, is speculative.

Even if TSCA were applied to this situation, there may be some limitations on how well it addresses the risk, depending again on your view of the risks.

Finally, the NIH guidelines and State tort law will play a quasi-regulatory role in this situation. The threat of lawsuits and the likelihood that the court will view the guidelines as a standard of care should provide incentive to those who would release genetically modified organisms into the environment to test them adequately and to get NIH approval beforehand.

Thank you.

[The prepared statement of Mr. Karny follows:]

STATEMENT OF

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CONGRESS OF THE UNITED STATES

BEFORE THE

SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY

AND THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

COMMITTEE ON SCIENCE AND TECHNOLOGY

UNITED STATES HOUSE OF REPRESENTATIVES

ON

REGULATING THE RELEASE OF GENETICALLY MODIFIED

ORGANISMS INTO THE ENVIRONMENT

JUNE 22, 1983

I am pleased to appear here today on behalf of the Office of Technology Assessment (OTA) to present our views on the current regulatory situation with respect to the release of genetically modified organisms into the environment for agricultural or industrial purposes.

Since the advent of recombinant DNA (rDNA) technology, there has been concern about potential risks as well as anticipation about promised benefits. Because novel organisms could be created, scientists and others wondered if they would have unexpected and dangerous properties. To address these concerns, the scientific community, aided by experts from other disciplines and by the public, developed guidelines for research involving rDNA. Two concepts underlie the guidelines: 1) rDNA research should be conducted at increasing levels of containment related to the degree of presumed hazard; and 2) the degree of oversight should be directly proportional to the degree of presumed hazard.

The guidelines were adopted by the National Institutes of Health in June 1976 and have been followed by the other Federal agencies funding rDNA research. Although the guidelines do not have the force of law, the private sector has adhered to them as far as we know. The adoption of the guidelines and favorable results in some early risk assessment experiments helped stay Congressional action to regulate rDNA research.

Today, experts are much less concerned about the risks presented by rDNA technology. As scientists gained more familiarity with the technology and learned more about molecular genetics, many of the postulated risks were seen to be unrealistic. This view was confirmed by specific risk assessment experiments. In addition, there have been no reported instances of injury to human health or the environment from rDNA products or organisms. As a result the containment requirements and oversight mechanism created by the original guidelines have been gradually but substantially reduced, and NIH has given serious consideration to their abolition.

Current regulation of rDNA processes and products consists of a combination of Federal laws designed to protect human health and the environment, the quasi-regulatory guidelines, and state and local health and environmental laws, including tort law. This regulatory system generally is viewed as adequate to address any risks presented by rDNA with the possible exception of the deliberate release of genetically manipulated organisms into the environment. Such organisms would include improved plants and possibly animals, as well as microorganisms designed to degrade pollutants, increase the recovery of oil from wells, or leach minerals from ores. I would like to address the remainder of my remarks to the case of deliberate release.

Why should we be concerned about the release of genetically modified organisms into the environment? Mankind has been genetically modifying plants and animals in a crude way for thousands of years. Are not the new techniques merely more sophisticated?

The various uses of genetically modified organisms that I have grouped under the phrase "deliberate release" appear to present different risks than other uses of organisms containing rDNA. First, there is the obvious but crucial difference that the organisms are not contained. Second, there are cases when some organisms have caused problems when introduced into an ecosystem for which they were not indigenous. Although only a fraction of "foreign" organisms ever establish an ecological niche and even less produce serious ecological disruptions, there are numerous examples where foreign species have successfully invaded and proliferated with serious consequences.[1] Nearly half of the major insect plant pests in the U.S. originated abroad. The gypsy moth, for example, was imported from Europe in the late 1800s for research purposes. Accidentally released, it now periodically defoliates large areas of trees in the Northeastern U.S. Another example is the intentional importation and release of starlings from Europe in the 19th Century; they now cause millions of dollars of crop damage and jet airliner crashes. Such examples also include microorganisms. Chestnut blight is a fungus that was brought into the U.S. on Asian plants. Although it causes little harm to its native host, it has essentially wiped out the American chestnut trees.[2] Kudzu is an imported weed that runs rampant in some of our Southern states.

How applicable is this experience to the use of genetically manipulated organisms in the environment? On one hand, it may not be too applicable. Since most major genetic changes are deleterious to the host organism, by making it less competitive in the environment, it may not be appropriate to compare genetically manipulated organisms to the ones mentioned above, which are especially well adapted to their environment. On the other hand, in order for genetically manipulated organisms to perform their tasks, they may have to be designed to be competitive with the indigenous ones and, therefore, might establish an environmental niche. Genetically manipulated oganisms that embody new properties never before found in those organisms may, when released into the environment, be like gypsy moths or chestnut blight. Thus, the risks presented by the deliberate release of novel organisms might be significantly greater than those presented by the use of DNA derived from nonpathogens in debilitated hosts and contained systems.

I'm sure the scientists who are testifying will provide more insight into this question. I raise it in order to help frame the policy question: Given this limited amount of information on risk, is the regulatory structure adequate? To address this question, I will outline the applicability of the following parts of the regulatory environment: 1) the NIH Guidelines; 2) Federal environmental statutes, particularly the Toxic Substances Control Act; 3) USDA administered plant and animal pest control statutes; and 4) relevant principles of tort law.

The NIH Guidelines

The guidelines apply to all research involving rDNA in the U.S. or its territories conducted at or sponsored by an institution receiving any support for rDNA research from NIH. The latest version can be found in the June 1, 1983 Federal Register.[3] The other Federal agencies conducting or funding rDNA research also require their scientists and grantees to comply. The guidelines are not binding on private companies unless the companies receive Federal funds for rDNA research. An exception is in those states or localities that have passed laws to require companies to follow the guidelines. As mentioned previously, the private sector has complied voluntarily.

The guidelines create an administrative framework that specifies the responsibilities of scientists, their institutions, and the Federal Government. For the institutions, the key organization is the Institutional Biosafety Committee (IBC), which oversees all rDNA work for compliance with the guidelines. At the Federal level, the key parties are the Director of

NIH, who is the final decision-maker under the guidelines, and the Recombinant DNA Advisory Committee (RAC), a diverse group of experts advising the Director in the major technical and policy issues involved.

The guidelines classify experiments into four categories: exempt, those requiring IBC notification at the time of initiation, those requiring IBC approval before initiation, and those requiring RAC review and NIH and IBC approval before initiation. For each category except the last, the guidelines specify physical and biological containment requirements. (Biological containment refers to the use of debilitated organisms or vectors.) Containment for work requiring NIH approval is set on a case-by-case basis.

Until this month, the guidelines did not apply to large-scale work with organisms containing rDNA, that is, cultures greater than 10 liters in volume. However, NIH had developed physical containment recommendations in 1980 for such work.[4] These became appendix K in the latest version of the guidelines.

With respect to deliberate release, the guidelines require that these experiments receive RAC review and NIH and IBC approval prior to initiation. The only exception is for certain plants described in Appendix L, added this month. In that case, experiments can be approved by a part of the RAC, called the Plant Working Group, without full RAC review.

From a regulatory perspective, there at least two potentially important limitations to the way the guidelines deal with deliberate release. Whether A these limitations are significant or not depends on one's view of the risks presented by deliberate release.

First, virtually all of the scientific experts on the RAC are molecular biologists or experts in human health. No one is an ecologist.[5] Some members are experts in plants, although at the October 1982 RAC meeting several members expressed the desire for background material on plant biology, and such material has been provided. It may be possible for RAC to overcome its limitation by drawing on the expertise of the Environmental Protection Agency and the Department of Agriculture which have nonvoting represenatives on the RAC.

The second potential limitation lies in the RAC review procedure itself. Proposals to do experiments requiring RAC approval are sent to NIH, which distributes copies to RAC members and publishes summary information in the Federal Register at least 30 days before the meeting. The nature and amount of information provided on the experiments is left to the discretion of the person requesting approval. Requests range anywhere from one page to several pages with attached scientific articles, although the RAC can and has requested more information. Decisions are then made at the meeting after whatever time individual RAC members have devoted to analyzing the request. In contrast, where there has been major concern about the risks presented by certain products, such as drugs or pesticides, a major comprehensive review of the product with respect to safety must be undertaken by the appropriate regulatory agency before the product can be marketed.

Federal Environmental Statutes Administered by EPA

The Environmental Protection Agency has extremely broad regulatory authority over most matters affecting the environment. Of the many statutes administered by EPA, the ones most relevant to deliberate release are the Toxic Substances Control Act, (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

TSCA authorizes EPA to acquire information on "chemical substances" in order to identify and evaluate potential hazards and then to regulate the production, use, distribution, and disposal of these substances. The heart of TSCA is a requirement that manufacturers of new chemical substances notify EPA ninety days before producing the substance and provide certain information about the chemical. The burden is then on EPA to prohibit or otherwise regulate the manufacture, sale, or disposal of the new chemical. This procedure is in contrast with that created by other health and safety statutes, such as FIFRA or the Federal Food, Drug, and Cosmetic Act, where the manufacturer has the burden of proving safety before the product can be marketed.

A "chemical substance" is defined under section 3(2)(A) of the Act as "any organic or inorganic substance of a particular molecular identity", including "any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature...." This would include DNA molecules; however, it is unclear whether the definition would encompass genetically modified organisms. One could argue that the definition encompasses living organisms because the language is quite broad, that Congress intended the definition to be broadly constructed, and that Congress intended TCSA to fill the gaps in the other environmental laws. On the other hand, because the definition refers to substances of "a particular molecular identity," it arguably does not encompass living organisms, the complete molecular compositions of which are not known and which may vary over time.

EPA itself has taken conflicting positions on this question. In promulgating its Inventory Reporting Regulations under TCSA on December 23, 1977, EPA took the following position in response to a comment that commercial biological preparations such as yeasts, bacteria, and fungi should not be considered chemical substances:

> "The Administrator disagrees with this comment.... This definition [of chemical substance] does not exclude life forms which may be manufactured for commercial purposes and nothing in the legislative history would suggest otherwise."[6]

However, in a December 2, 1977 letter responding to a Senate inquiry, EPA Administrator Douglas M. Costle stated the following:

> [A]lthough there is general consensus that recombinant DNA molecules are "chemical substances" within the meaning of section 3 of TSCA, it is not at all clear whether a host organism containing recombined DNA molecules fits--or was intended to fit--that definition.... If such organisms are subject to TCSA on the grounds that they are a "combination of.... substances occurring in whole or in part as a result of a chemical reaction," the Agency might logically have to include all living things in the definition of "chemical substance"--an interpretation which I am confident that Congress neither contemplated nor intended.[7]

Recently, a draft policy paper prepared by EPA's Office of Toxic Substances took the position that TSCA applies to such organisms. At the time, this position was not official EPA policy.

If EPA were to take the broader interpretation (and assuming that interpretation were to survive any subsequent legal challenge), TCSA would have great potential for regulating the deliberate release of genetically modified organisms. Under section 4 of TCSA, EPA can adopt rules requiring testing of chemical substances that "may present an unreasonable risk of injury to health or environment" (or will be produced in substantial quantities and enter the environment in substantial quantities or result in substantial human exposure) when existing data is insufficient to make a determination and testing is necessary to develop adequate data. Section 5 requires the manufacturer of a new chemical substance to notify EPA ninety days before beginning production and submit any test data it may have on the chemical's health or environmental effects. If the EPA decides that the data is insufficient for evaluating the chemical's effects and that it "may present an unreasonable risk of injury to health or the environment" or will produced in substantial quantities, it can propose an order to restrict or prohibit the new chemical substance's manufacture or use. Finally, under section 6, EPA can prohibit or regulate the manufacture or use of any chemical substance that "presents, or will present an unreasonable risk of injury to health or the environment."

The scientific evidence probably does not support a finding that most genetically modified organisms present an unreasonable risk. On the other hand, the lower standards in sections 4 and 5 ("may present an unreasonable risk") and the premanufacturing notice requirement probably would permit EPA to evaluate cases in which such organisms were proposed to be released into the environment.

TSCA also provides for record keeping and information gathering. Section 8(a) gives EPA authority to require companies (other than small manufacturers) to "maintain such records and ... submit ... such reports as [EPA] may reasonably require." These records or reports may include, insofar as known to the company or reasonably ascertainable, existing data concerning the environmental and health effects of the chemical substances. In addition, Section 8(a) requires the manufacturer, processor, and distributor of a chemical substance to "maintain records of significant adverse reactions to health or the environment alleged to have been caused by the substance", and, if they obtain information "which reasonably supports the conclusion that each substance or mixture presents a substantial risk of injury to health or the environment," Section 8(e) requires them to inform EPA of the information.

Despite its theoretical applicability, TCSA may leave much to be desired in terms of a practical program to regulate the use of genetically engineered microorganisms in the environment. First, EPA has little expertise or experience in genetic engineering. Second, its toxic substances program has been significantly understaffed, according to a 1980 GAO study.[8] Third, TSCA may not give EPA sufficient regulatory power, if the risks presented by deliberate release are viewed as substantial. For example, Section 5, which creates the premanufacturing notice requirement, does not require the generation of toxicological data. A recent OTA study found that nearly half of the premanufacturing notices submitted to EPA do not have information about the chemical's toxicity.[9] As to the importance of such information, the report stated:

> Certainly, the absence of toxicity data complicates EPA's efforts to decide whether a new chemical may present an unreasonable risk to health or the environment. But the importance of toxicity data for making decisions about particular chemicals varies. Those data are less important for chemicals that closely resemble others for which there is much information and experience. They are critical for unusual chemicals or chemicals for which there is limited information.[10]

Moreover, the burden is on EPA to take legal action if it believes that insufficient data exists for a new chemical substance. In contrast with FIFRA, which requires a showing of safety, TSCA does not require that safety studies be conducted in support of a premanufacturing notice.

TCSA does not apply to pesticides, which are covered by FIFRA. If genetically manipulated organisms are used as pesticides, there is no uncertainty regarding EPA's ability to regulate them. FIFRA creates a premarketing clearance procedure under which EPA reviews data on safety and efficacy and then registers the pesticide. EPA has proposed a rule on data requirements for such registration.[11] Sections 158.65 and 158.165 cover biological pest control agents, including genetically manipulated ones. The sections set extensive data requirements on product performance, toxicology, residue analysis, hazards to nontarget organisms, and environmental fate and expression. These requirements attest to the importance and difficulty of evaluating the ecological impacts of novel organisms. They represent the thinking of the staff people who regulate biological pesticides, and they probably represent the most sophisticated analysis available on how to evaluate the ecological impacts of new organisms, including genetically modified ones.

USDA Plant and Animal Quarantine Laws

The USDA regulates the importation and interstate shipping of plants, animals, and their pathogens. The relevant statutes include The Plant Quarantine Act (7 U.S.C. §§ 151-167), the Federal Plant Pest Act (7 U.S.C. §§ 150aa et. seq.), and 21 U.S.C §§ 101-135 for animals. I am not familiar enough with these statutes to assess whether they would apply to deliberate release and, what their advantages and disadvantages would be. I assume the USDA representative will address this issue.

Tort Law

A tort is a civil wrong, other than a breach of contract, for which a court will award damages or other relief. Two well known examples are automobile injury and medical malpractice cases.

This body of law is important because it is flexible, judge-made law, applied on a case-by-case basis. If necessary, it is available to fill any gaps in the present patchwork system regulating biotechnology, particularly with respect to deliberate release. Although tort law functions primarily to compensate injury, the large dollar amounts that can be involved should be incentive for safety conscious conduct. Thus, tort law can serve a regulatory function. The most applicable concepts of tort law are negligence and strict liability.

Negligence is conduct (an act or omission) that falls below a standard established by the law for the protection of others against unreasonable risk of harm. These standards are developed by the courts in the course of hearing many cases.

Because genetic engineering is so new and apparently has caused no harm, there have been no lawsuits claiming injury due to negligence. If one were to arise, a crucial issue would be the standard of care against which the defendant's conduct would be measured. The court would undoubtedly look first to the NIH guidelines. Noncompliance with the guidelines would support a finding of negligence. However, it would be a mistake to assume that compliance would be sufficient to prevent a finding of negligence in any future lawsuit, since other evidence may indicate that a higher degree of care was required. In fact, because the guidelines are directed mainly toward protecting human and animal health, they would not be as relevant or persuasive as Federal environmental laws and regulations in a lawsuit claiming ecological damage caused by a genetically modified organism. For example, if a deliberately released organism such as a pollution degrading microbe turned out to be pathogenic for corn, the best evidence for the required amount of testing for adverse environmental impacts probably would be EPA's proposed rule for registering pesticides, because, as discussed previously, this is the best overall model for the amount of testing required.

Unlike negligence, strict liability does not require a finding that the defendant breached a duty of care to the injured person; the fact that the defendant's actions caused the injury is enough to impose liability regardless of how carefully the activity was done. This concept applies to activities characterized as "abnormally dangerous." However, the courts have been fairly liberal in determining what is abnormally dangerous.

In cases involving products sold commercially, a somewhat different and less restrictive standard of strict liability is applied. Basically, such lawsuits can be brought against a manufacturer, distributor, or seller of a product -- in this case a genetically modified organism released into the environment -- if the product had a defective condition, making it unreasonably dangerous and if it causes physical harm. Various factors are weighed in determining if the product is unreasonably dangerous: the product's utility, the likelihood of injury, the availability of safer alternatives, the manufacturer's ability to eliminate the hazard, and the user's ability to avoid injury. The threat of such product liability suits will likely provide great incentive for manufacturers of genetically modified organisms for environmental uses, such as pollution control, to test them rigorously before sale.

Conclusion

With the exception of FIFRA, there is no Federal law that clearly covers the deliberate release of genetically modified organisms into the environment. TCSA has the potential to be applied, and the consensus seems to be developing that such organisms are included within the Act's definition of chemical substance. Whether or not the courts would uphold such an interpretation upon any subsequent legal challenge cannot be predicted with certainty. Even if TCSA is applied, there would be some limitations on how well it addresses the risks.

The NIH guidelines and state tort law will play a quasi-regulatory role with respect to deliberate release. The threat of lawsuits and the likelihood that the court will view the guidelines as the standard of care should provide incentive for those who would release genetically modified organisms into the environment to test them adequately beforehand.

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Project Director, OTA Assessment of The Role of Genetic Testing in the Prevention of Occupational Disease (October 1981 - April 1983)

Staff Attorney, OTA Assessment of Impacts of Applied Genetics: Microorganisms, Plants, and Animals (December 1979 - September 1981)

ATTORNEY, U.S. SECURITIES AND EXCHANGE COMMISSION, Washington, D.C.
September 1973 - December 1979

Senior Attorney, Division of Corporation Finance (August 1976 - December 1979)

Staff Attorney, Division of Corporation Finance (September 1973 - July 1976)

PUBLICATONS:

Books

Karny, Newell, Rose, and Williams, The Role of Genetic Testing in the Prevention of Occupational Disease, Office of Technology Assessment (Washington, D.C.: GPO 1983).

Contributions to Books

"Regulation of Genetic Engineering," in Impacts of Applied Genetics: Microorganisms, Plants, and Animals, Office of Technology Assessment (Washington, D.C.: GPO 1981), pp. 211-234.

"Patenting Living Organisms," in Impacts of Applied Genetics, pp. 237-254.

"History of the Recombinant DNA Debate," in Impacts of Applied Genetics, pp. 315-319.

"Constitutional Constraints on Regulation," in Impacts of Applied Genetics, pp. 320-321.

"Revisions in Patent Law and the Patent Court System Affecting the Patenting of Life Forms," G. Bernard, N. Noonan, and G. M. Karny, in Banbury Report 10: Patenting of Life Forms (New York: Cold Spring Harbor Laboratory 1982), pp. 285-320.

Articles

"Regulation of Genetic Engineering: Less Concern about Frankensteins but Time for Action on Commercial Production," 12 U. Tol. L. Rev. 815 (1981).

"Regulation of Genetic Engineering in the Food and Agriculture Industries" 4 Recombinant DNA Tech. Bull. 152 (1981).

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"Recombinant DNA Guidelines and Environmental Concerns," Genetic Engineering News (March/April 1982), p.6.

"Biotechnology: The Regulatory and Legislative Environment," 5 Recombinant DNA Tech. Bull. 127 (1982).

EDUCATION:

NEW YORK UNIVERSITY SCHOOL OF LAW, J.D., 1973

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PROFESSIONAL ASSOCIATIONS:

District of Columbia Bar Association
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Mr. Gore. Thank you. This is a fascinating panel. I hardly know where to begin.

Let me recognize my cochairman, Mr. Walgren.

Mr. Walgren. Thank you, Mr. Chairman.

I wonder if any of the panelists, and perhaps particularly Dr. Sharples and Dr. Alexander, could expand on the potential of risk assessment. From your testimony, it is pretty clear, as Dr. Sharples says, that we cannot predict, that it is an unknown. Dr. Alexander says that clearly there just has not been an effort in prediction, at least in a disciplined research way.

This committee has been interested in whether or not it is possible to develop model risk assessments so that the public and others could make at least a ball park judgment about whether or not the agencies have been making proper judgments or any proposal has been looked at carefully in a proper way.

What are the potentials and what are the limitations of what at least I as a layman think exists, known as risk assessment?

Dr. Alexander. If I might go back to the five factors I mentioned earlier, I think in three instances—the probability of risk, the probability of survival and the probability of growth—we can do risk assessments. We are able now to devise meaningful tests, and in a reasonably short time we can determine the possible components of risk and, in fact, develop a sensible regulatory program.

As far as effects, I think that I agree completely with Dr. Sharples in that we have no histories. You are asking, in effect, a scientist to predict the outcomes of a nonexistent field of speculation. It has not been done before. We have no basis of even devising a good laboratory testing procedure for Noah's Ark. What species do we look at? All of them, two by two?

We need to have some kind of approach to assessing ecological consequences. This has not been done by NIH. It has not been done by USDA, and it has not been done by EPA or Interior, because we have never had those questions before.

Our approach has been to contain. We call that quarantine. However, if there is a release from a quarantine, we cannot predict, as Dr. Sharples said, the outcome. We cannot do risk assessments. We cannot even do a test at this time.

Mr. Walgren. Can you add anything to that?

Dr. Sharples. Not really. I have done some work at Oak Ridge on trying to develop a reasonable test for the effect of a chemical on an ecosystem. In this case it was a soil community. We took natural soil and we contaminated it with a chemical.

As soon as you get beyond the level of taking a single organism in a pure culture, it is very difficult to interpret the results you get. You just cannot follow what is going on at all the different levels with all the different organisms in an ecological community.

Now I realize that what we are telling you is that there is no way to do this. That is probably not what you want to hear.

Certainly, it is possible that you could advance the field of risk assessment by doing some model ecosystem-type things, but there is no way that you can test every conceivable variety of microorganismal community.

Mr. Walgren. However, there would be a way to classify things as—I guess when the harm is great, the least risk is the ultimate threat, isn't it? That, I guess, is the problem.

When we went through this concern over the release of genetic engineering, there were the proposed restrictions and then the academic community became satisfied that this was not all that dangerous and, therefore, we could calm down a little bit.

Mr. Gore. That was the controversy over recombinant DNA research in the laboratory, and the concern essentially focused on the possibility that newly created organisms might escape from the laboratory and proliferate in ways that did damage.

The conclusion of the scientific community, as well as the political community, has been that those concerns were probably overblown, greatly overblown, and the regulations that have been put in place have satisfied most everyone.

In this case, the difference is that all of those regulations, safeguards, and precautions were based upon the principle of containment. Here we are talking about new organisms that are going to be purposefully introduced into the environment with yet unknown consequences for the ecosystem.

Mr. Walgren. Now my question is this: In response to that concern before the scientific community became satisfied that they need not be overly concerned, when that concern was high, was there an adequate response in the scientific community to develop risk assessment in that context, or did we just become comfortable with the ways that were proposed to deal with handling that research and, therefore, forget about the problem?

Dr. Alexander. I think Mr. Karny has highlighted the general questions that came up at that point by saying that the RAC committee of NIH is populated by molecular biologists and geneticists. In fact, at that time, if one looks back at the congressional hearings and at the local hearings, there was no real ecological question addressed at that point.

I do not quite agree with the chairman that the scientific community was polled and thought that there was no problem. I think there is likely to be little public health problem as long as containment works; conversely, as I mentioned, if containment does not work, and surely it will fail in some cases, we may have some undesirable changes.

Second, if you release the organisms, do we have ecological consequences? At that time the issue was never really addressed.

Mr. Gore. If my colleague will yield, I do not believe that I said that the scientific community was polled and felt there was no problem. What I said was that the scientific community, which had initiated the concerns about the possibility of escape during laboratory experiments, now feels that those concerns were overblown. Indeed, the individual scientists who signed the famous letter that started that whole process now, almost to a person, feel that, although they might not have been wrong in triggering that concern, they were very responsible, and you want to err on the side of safety when civilization ventures into this realm of the unknown, but they now feel that the response was more than adequate.

Dr. Sharples. If I might just make one more comment, at least I do not want to give the impression that what I am saying is the risks are so great that we should stop the research. I do not think that is really appropriate.

As Dr. Alexander and I also pointed out, the risks are small. The point is that we should not rush into this. We should try——

Mr. **Walgren**. However, the question I have is, given the risk, should we start the research in assessment models and in pursuit of being able to predict and anticipate what might happen?

Dr. **Sharples**. Yes. I think a best guess is better than nothing at all.

Mr. **Walgren**. Then my question is, Have we adequately responded on that level of trying to reasonably make the assessments? I hear Dr. Alexander saying that really not much attention has been given to this.

Dr. **Alexander**. I, too, repeat what Dr. Sharples has said. I think we do have a low risk; but the low risk may be linked with a major effect. We should not prevent the research from going on. We do not have testing procedures now to develop a risk assessment. We have no numbers to put into it. However, I think the research can be done—it has not been yet done, but it can be done—in order to develop meaningful figures, in order to do a risk assessment and to know where there will be likely hazards.

Mr. **Walgren**. One other subject, if I may, Mr. Chairman.

Dr. Sharples indicates in her testimony—or underscores the idea—that the changes that make a organism resistant to pesticides are really linked to one gene, and that when an organism can change three genes in sequence, that is a multiplication of the resistance factor by three.

How difficult is it to keep up with these resistance changes in organisms? If an organism becomes resistant to whatever methods we are using to control it, by simply shifting one point in the system, how far behind are we at being able to catch up to that shift and achieve the same result that we used to have with a different mechanism?

Dr. **Alexander**. The best examples of this are in diseases of our major grain crops. There are regular genetic changes in disease organisms of corn and wheat. We are always behind because we cannot predict the nature of the change, but we are not very far behind because we continue to produce a lot of grain.

In that case, with organisms that we are monitoring, we can do a good job. In organisms that we have not monitored before, that we have no history of your guess is as good as mine.

Mr. **Walgren**. Thank you, Mr. Chairman.

Mr. **Gore**. Congresswoman Schneider?

Mrs. **Schneider**. No, thank you. I have no questions.

Mr. **Gore**. Congressman Brown?

Mr. **Brown**. Aren't we already introducing genetically engineered organisms into the environment on a large scale?

Dr. **Alexander**. Not genetically engineered organisms in the modern sense. We are introducing organisms in agriculture, for example, some which are modified somewhat, but these are all naturally occurring species essentially.

Mr. **Brown**. An example that I have in mind is, for example, the release of billions of sterilized fruit flies in California last year. These were genetically modified.

We have a number of commercial enterprises that are offering genetically modified organisms which distort the life cycle of certain pests, and by breeding with them hopefully keep the pests under control.

There are some firms in California that I think are offering that kind of commercial service now.

I am trying to distinguish between what they are doing now and what we are talking about here. Is there a sharp line of demarcation that can be drawn or is this not a rather difficult boundary to conceptualize?

Dr. ALEXANDER. Mr. Brown, I think you have highlighted what to me is the clear difference. Prior to the release of these organisms—and you are quite correct, these are modified in some way, genetically modified—in fact, they have been all tested very carefully beforehand, because they are designed for pest control. They are, I think, included under FIFRA. There have been very careful tests. We know before the release that there are no problems.

I do not think that one wants to have that extensive a testing program with regard to all of the genetically engineered organisms, because it will entail enormous expenses. I would expect that that kind of regulation would markedly deter the development of what I consider to be a very good industry, the genetic engineering industry.

One can have modest testing to determine whether there are, in fact, potential hazards with other organisms besides the BT, as it is referred to, and the sterile male insects.

Mr. BROWN. Now we had some rumors in connection with the release of the sterile males that maybe one or two unsterile males slipped through and resulted in residual outbreaks. I do not know how good the testing, the quality control, or the legal regulatory framework was in these cases, although we have studied them a little bit. I am just trying to draw some comparisons here on which we can erect a structure of regulatory concern.

You, in listing these five risk components, this sort of leads to the thought that each of these becomes sort of a gate. If, for example, the possibility can be tested that the organism will survive and you find that it will not survive in a normal environment, then you do not need to go through the other risk assessments.

Dr. ALEXANDER. Yes, sir; that is right.

Mr. BROWN. I wonder, in thinking through this process, how complex the overall risk assessment might be. Of course, as all of you indicate, we have not experimented with this yet. We do not really know. However, you see no conceptual reason why we could not erect a risk assessment process, taking these one at a time, and do at least as well as we do with some of our present risk assessment processes?

Dr. ALEXANDER. I believe that risk factors 1, 2, and 3 are very low cost assessment programs. I could not even hazard a guess as to how expensive 4 and 5 would be, simply because we have no information on this. My guess is that most organisms will, in fact, fail in the—they will have zero risk in components 1, 2, and 3. However, as Mr. Gore pointed out, we are concerned now with the organisms we are deliberately introducing. If they do a job in the environment, then automatically we have answered components or risk factors 1, 2, and 3, and we are into 4.

I think we do have to have some more sensible program, and it may be so expensive that, in fact, the regulations will seriously affect the development of the industry. This, I would hope, is not the case.

Mr. GORE. Congressman Volkmer?

Mr. VOLKMER. I have no questions.

Mr. GORE. I think my colleagues have covered it very well, and your testimony certainly has covered it extremely well, but let me just ask you a couple of brief questions.

The key to whether or not TSCA covers these entities, Mr. Karny, is whether or not we can define new life forms as "chemical substances;" is that correct?

Mr. KARNY. Yes; that is correct.

Mr. GORE. EPA has a very lengthy statement on that matter a little bit later on, but it may well come under TSCA.

Dr. Sharples, from your work—let me just give you my understanding of what we are dealing with here. When a substance is newly engineered and introduced into the environment, the likelihood that it will proliferate and cause unforeseen damage is lower than that associated with an imported species from another environment because in that case, the starling or kudzu, or whatever, it was already the result of a very long evolutionary engineering process which predetermined a certain survivability, persistence, aggressiveness, and whatever.

However, the fact that the likelihood of proliferation is lower does not exclude the very real possibility that some of these newly-engineered substances do, in fact, possess the same characteristics that these other imported species do. When they are purposefully engineered to sustain themselves in the environment in order to accomplish the specified task, that likelihood is again elevated.

Does all that fit in with your analysis? Let me ask you to be brief in your response because we have a vote on the floor.

Dr. SHARPLES. More or less. Is that brief enough? [Laughter.]

Mr. GORE. Well, tell me where I am going wrong. [Laughter.]

Dr. SHARPLES. It was such a long question, I am not sure I know what you are asking.

Mr. GORE. I am trying to extrude the lessons from your study.

Dr. SHARPLES. OK. Let me make one point.

Organisms in general—you can talk about organisms in terms of being similar to each other or not similar. By that, I mean that they are capable of living in the same general environment. You would not expect, say, a soil bacterium to do well in an aquatic community.

Mr. GORE. Yes.

Dr. SHARPLES. I am trying to answer your question. I am sorry. Could you——

Mr. GORE. You have said it is hard to equate, it is hard to draw lessons from these imported species and apply them precisely to newly engineered organisms.

Dr. SHARPLES. What I was getting at was that if you did not want your organism to survive in the water, you would probably not use an aquatic organism, which is more likely to survive because that is the environment it is from.

I am not sure that there is any way that you can know that a foreign organism, an exotic organism, is evolutionarily better off than a manmade one in general. It really depends on what environment you are dealing with, what organism. If there is a match, that is really the appropriate thing. If there is not a match, then——

Mr. GORE. Very good. May we submit additional questions to the three of you in writing, if we have some? Thank you very much.

We will go vote on the floor. When we come back, we will go the second panel.

I would really like to thank the three of you for getting us off to a good and fascinating start. You really covered the territory very, very well. We appreciate it.

We will come back in about 10 minutes.

[Recess.]

Mr. GORE. The subcommittees will come back to order.

Our second panel is made of Dr. Ananda Chakrabarty, from the Department of Microbiology at the University of Illinois Medical Center in Chicago; Dr. Steven Lindow, with the Department of Plant Pathology at the University of California, Berkeley; and Dr. Ralph Hardy, director of life sciences research with E. I. du Pont Co., Inc., in Wilmington, Del.

If the three of you would come forward to the witness table, we will get the second panel underway.

We are delighted to have you as guests today and will be delighted to hear your testimony.

Again, without objection, your prepared statements will be included in full in the record. If you wish to summarize any portion of your statements, we will be delighted for you to do that.

We will hear first from Dr. Ananda Chakrabarty with the Department of Microbiology at the University of Illinois Medical Center.

Doctor, it is a pleasure to have you here. I am sure you are quite used to the fact that your name is attached to the history of this whole science now with the famous Supreme Court decision. It makes you something of a celebrity in this arena. Thankfully for us, you retain your expertise. We want you to share it with us here today. We look forward to your testimony.

STATEMENT OF DR. ANANDA CHAKRABARTY, DEPARTMENT OF MICROBIOLOGY, UNIVERSITY OF ILLINOIS MEDICAL CENTER, CHICAGO, ILL.

Dr. CHAKRABARTY. Thank you, Mr. Chairman.

I would like to thank all of you for giving me this opportunity to express my views before this august body on topics related to the use of gentically engineered micro-organisms in an open environment.

As you are all aware, there are specific guidelines stipulated by NIH that dictate the level of physical or biological containment in the preparation and large-scale production of useful drugs and pharmaceuticals such as insulin, human growth hormone, interferon, et cetera. Production of such bacteria, and the level of their accidental release in an open environment, can be stringently controlled by appropriate physical containment. There are, however, other reasons why we might be interested in deliberately releasing genetically manipulated bacteria in an open environment. I will illustrate this point by giving you examples of two research areas that we are pursuing at the University of Illinois at Chicago which will necessitate the application of any micro-organism we develop in an open environment.

The first one is the area of toxic chemical pollution. Undoubtedly, you are aware of the potential health hazards posed by the presence of a large number of toxic chemical dumpsites all over the country. Many of the buried drums containing the toxic chemicals get corroded over a long period of time, and the released chemicals move downward to contaminate the aquifers from which we derive our drinking water or move up and contaminate the surface, leading to poisoning of human beings and animals.

In addition, deliberate or inadvertent release of toxic chemicals often leads to human contamination—as the cases in Love Canal, Seveso, and Times Beach will exemplify.

Unfortunately, we have no technology that allows purification of contaminated soil, so that the only thing we can do is to ban the production or usage of the chemicals and evacuate people from the contaminated areas. This, of course, does not address the problem of how to get rid of the chemicals from the area of contamination.

Since micro-organisms traditionally have been responsible for recycling the natural wastes and maintaining the carbon, nitrogen, and sulfur cycle in nature, it is the inability of the natural microflora to biodegrade synthetic chemicals that has led to the present-day toxic chemical pollution problem.

Yet, I feel that microbial genetic engineering can play a role in solving some of these problems. As an example, I would like to cite the development in our laboratories of a bacterial strain that can utilize 2,4,5-T, a major component of agent orange, as a sole source of carbon and energy. This bacterium has been demonstrated to remove large concentrations of 2,4,5-T, 10,000 to 20,000 parts per million, from heavily contaminated soil within a few weeks. Removal of the 2,4,5-T allows the soil to support growth of broad-leaf plants, which are sensitive to the presence of low concentrations, let's say about 15 or 20 parts per million or less, of 2,4,5-T. Once the 2,4,5-T is gone, the bacteria die off within a few weeks, becoming undetectable after a couple of months. Since no naturally-occuring micro-organisms, pure or mixed, are known to utilize 2,4,5-T as a sole source of carbon, such experiments appear to raise hope that laboratory-developed bacterial strains may be effective in removing at least some of the priority toxic chemicals from the environment.

How effective are the genetic techniques for developing similar cultures for other types of pollutants? This brings me to the question of the use of micro-organisms in tertiary oil recovery. By preparing genomic libraries with cosmid vectors capable of propagating in a large number of gram negative bacteria, and under strong selective pressure in continuous cultures where such cloned genes are transferred to various other bacteria, it has also been possible to develop a mixed culture that can grow with dibenzothiophene as a sole source of carbon and sulfur. I mention dibenzothiophene because it is a major source of sulfur in many varieties of high sulfur coal and oil, burning of which is thought to lead to problems of acid rain in the northeast part of the United States and Canada.

The commercial implications of using microbial technology for desulfurization or enhanced recovery of oil are enormous. Our laboratory has developed micro-organisms that can utilize solid straight-chain hydrocarbons, but are unable to utilize liquid straight-chain hydrocarbons. Ostensibly such cultures can be used for the removal of high molecular weight paraffins from high paraffin oil leaving the liquid fuel hydrocarbons behind.

Surfactants, produced by such cultures, also appear to greatly decrease the viscosity of heavy oil, decrease surface tension at the oil/water interface, and lead to release of oil from tar sands. There are, however, no specific guidelines that regulate the release of micro-organisms in an open environment, either for toxic chemical clean-up or oil recovery. Well-defined guidelines, not necessarily legislation, would be very useful in allowing an evaluation of the effectiveness of this emerging microbial technology.

Recognizing that such research is being conducted by small companies, legislation to allow tax incentives for research and development in the area of energy and pollution control, and an expeditious review of application of genetically engineered micro-organisms and related products by regulatory agencies such as the Environmental Protection Agency, would be very helpful.

In addition, limited legal liability for the use of genetically engineered micro-organisms is, at least initially, a necessity to allow appropriate field trials to be conducted in toxic chemical dumpsite areas or oil well areas. I hope this hearing will form the basis to enable the committees to draw up a few of such guidelines.

Thank you.

[The prepared statement of Dr. Chakrabarty follows:]

Honorable Mr. Chairman Gore, Mr. Chairman Walgren, and members of the Subcommittees:

I would like to thank you for giving me this opportunity to express my views before this august body on topics related to the use of genetically-engineered microorganisms in an open environment. As you are all aware, there are specific guidelines stipulated by NIH that dictate the level of physical or biological containment in the preparation and large scale production of useful drugs and pharmaceuticals such as insulin, human growth hormone, interferon, etc. Production of such bacteria, and the level of their accidental release in an open environment, can be stringently controlled by appropriate physical containment. There are, however, other reasons why we might be interested in deliberately releasing genetically-manipulated bacteria in an open environment. I will illustrate this point by giving you examples of two research areas that we are pursuing at the University of Illinois at Chicago which will necessitate the application of any microorganism we develop in an open environment . The first one is the area of toxic chemical pollution. Undoubtedly, you are aware of the potential health hazards posed by the presence of a large number of toxic chemical dump sites all over the country. Many of the buried drums containing the toxic chemicals get corroded over a long period of time, and the released chemicals move downward to contaminate the aquifers from which we derive our drinking water or move up and contaminate the surface, leading to poisoning of human beings and animals. In addition, deliberate or inadvertant release of toxic chemicals often leads to human contamination---as the cases in Love Canal, Seveso and Times Beach will exemplify. Unfortunately, we have no technology that allows purification of contaminated soil, so that the only thing we can do is to ban the production or usage of the chemicals, and evacuate people from the contaminated areas. This, of course, does not address the problem of how to get rid of the chemicals from the area of contamination. Since microorganisms traditionally have been responsible for recycling the natural wastes and maintaining the carbon, nitrogen and sulfur cycle in nature, it is the inability of the natural microflora to biodegrade synthetic chemicals, that has led to the present day toxic chemical pollution problem. Yet, I feel that microbial genetic engineering can play a role in solving some of these problems. As an example, I would like to cite the development in our laboratory of a bacterial strain that can utilize 2,4,5-T, a major component of Agent Orange, as a sole source of carbon and energy. This bacterium has been demonstrated to remove large concentrations of 2,4,5-T (10,000-20,000 ppm) from heavily contaminated soil within a few weeks. Removal of the 2,4,5-T allows the soil to support growth of broad-leaf plants, which are sensitive to the presence of low concentrations (15 to 20 ppm or less) of 2,4,5-T. Once the 2,4,5-T is gone, the bacteria die off within a few weeks, becoming undetectable after a couple of months. Since no naturally-occurring microorganisms, pure or mixed, are known to utilize 2,4,5-T as a sole source of carbon, such experiments appear to raise hope that laboratory-developed bacterial strains may be effective in removing at least some of the priority toxic chemicals from the environment.

How effective are the genetic techniques for developing similar cultures for other types of pollutants? This brings me to the question of the use of microorganisms in tertiary oil recovery. By preparing genomic libraries with cosmid vectors capable of propagating in a large number of gram negative bacteria, and under strong selective pressure in continuous cultures where such cloned genes are transferred to various other bacteria, it has also been possible to develop a mixed culture that can grow with dibenzothiophene as a sole source of carbon and sulfur. I mention dibenzothiophene because it is a major source of sulfur in many varieties of high sulfur coal and oil, burning of which is thought to lead to problems of acid rain in the northeast part of the United States and Canada. The commercial implications of using microbial technology for desulfurization or enhanced recovery of oil are enormous. Our laboratory has developed microorganisms that can utilize solid straight-chain hydrocarbons, but are unable to utilize liquid straight-chain hydrocarbons. Ostensibly such cultures can be used for the removal of high molecular weight paraffins from high paraffin oil leaving the liquid fuel hydrocarbons behind. Surfactants, produced by such cultures, also appear to greatly decrease the viscosity of heavy oil, decrease surface tension at the oil/water interface, and lead to release of oil from tar sands. There are, however, no specific guidelines that regulate the release of microorganisms in an open environment either for toxic chemical clean up or oil recovery. Well-defined guidelines, not necessarily legislation, would be very useful in allowing an evaluation of the effectiveness of this emerging microbial technology. Recognizing that such research is being conducted by small companies, legislation to allow tax incentives for research and development in the area of energy and pollution control, and an expeditious review of application of genetically engineered microorganisms and related products by regulatory agencies such as the Environmental Protection Agency would be very helpful. In addition, limited legal liability for the use of genetically engineered microorganisms is, at least initially, a necessity to allow appropriate field trials to be conducted in toxic chemical dump sites or oil well areas. I hope this hearing will form the basis to enable the committees to draw up a few of such guidelines.

Respectfully submitted,

A M Chakrabarty
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Professor of Microbiology
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CURRICULUM VITAE

Ananda M. Chakrabarty

PERSONAL DATA

Position: Professor of Microbiology, University of Illinois Medical Center, Chicago, Illinois 60612
Birthdate: April 4, 1938
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EDUCATION

B.Sc.	St. Xavier's College, Calcutta, 1958
M.Sc.	(Biochemistry), University of Calcutta, 1960
Ph.D.	(Biochemistry), University of Calcutta, 1965

RESEARCH EXPERIENCE

Research Associate and Visiting Lecturer, University of Illinois, Urbana, 1965 - 1971.
Staff Member, GE Research and Development Center, Schenectady, 1971 -1979.
Adjunct Professor of Biology, State University of New York, Albany, 1976 - 1979.

HONORS

IR-100 award, Chicago, 1975.
Selected Industrial Research 'Scientist of the Year' 1975, Chicago, IL

MAJOR RESEARCH INTEREST

Pseudomonas Infection in Cystic Fibrosis; Plasmids and biodgradation of synthetic toxic chemicals.

PROFESSIONAL ACTIVITIES

Participated in Asilomar and La Jolla Recombinant DNA Conferences to develop guidelines for Recombinant DNA research
Acted as a Chairman or presented talks in the workshops and Symposia on Genetic Engineering organized by the National Academy of Sciences, Society of Industrial Microbiology, Committee on Genetic Manipulation, European Molecular Biology Organization (EMBO) etc.
Member, Editorial Board, Journal of Bacteriology
Member, Editorial Board, Petroleum Microbiology
Consultant, United Nations Committee on the Application of Genetic Engineering in Developing Nations (UNIDO, Vienna)
Member, NIH Study Section of Microbial Genetics

Mr. GORE. Thank you very much. We will hold our questions until our other two witnesses have testified.

Dr. Steven Lindow, with the Department of Plant Pathology at the University of California at Berkeley, is our next witness.

We are delighted to have you here, Doctor. Please proceed.

STATEMENT OF DR. STEVEN E. LINDOW, DEPARTMENT OF PLANT PATHOLOGY, UNIVERSITY OF CALIFORNIA, BERKELEY, CALIF.

Dr. LINDOW. Thank you, Mr. Chairman.

I have submitted a possibly painfully detailed report on some of the specific details of what we have been doing in plant pathology in California, and specifically relating to an important crop production problem in agriculture.

As a plant pathologist, I studied frost injury to plants. We have now found that frost injury, which is a very important production problem—it is a major limiting problem in many areas. Although frost injury is a variable amount throughout the years, it is estimated that damage resulting from frost injury amounts to some hundreds of millions of dollars, up to about $3 billion per year, in the United States. The worldwide problem is much greater than that.

In addition to the direct losses due to frost injury, growers also spend many millions of dollars in trying to prevent frost injury by various ways. Many of these methods of frost prevention, including the burning of fossil fuels, are both expensive and degrade environmental quality.

As a plant pathologist, we have been looking at the reasons for frost injury to plants and ways that we might try to control them; thus, increasing agricultural productivity.

Making a long story much shorter, we have found that certain bacteria that live on the surfaces of healthy plants cause those plants to be very much more frost sensitive than they otherwise would be; that is, plants have to have ice formation within their tissues to allow damaging ice formation to occur.

We have two species of bacteria which are very prevalent among all healthy plants in nature and have the ability to catalyze ice formation. They act as little ice crystals and to allow ice formation to occur in these plant tissues. The water does not have to occur at very warm temperatures. The ice will not form in water at temperatures close to 32 degrees, as most of us consider, but the water can remain in a liquid state to very cold temperatures.

Thus, one of our goals, then, has been to avoid these bacteria that are present on leaves that cause ice catalysis, the formation of ice on plant tissues.

One outgrowth of this, then, is an alternate method of frost control to plants.

As I mentioned, two species of bacteria seem to be the only ones that are of primary importance in the catalysis of ice formation, and, thus, causing frost injury to plants. These bacteria, though, are very widely distributed. Almost all healthy plants have at least some of these bacteria present on their leaves.

Our goal, then, has been to rid these plants of these bacteria. The method that I would like to address today has been the use of competing micro-organisms. We have found that by applying certain micro-organisms to plants before they are "contaminated" with these detrimental ice nucleating bacteria, we can largely prevent those plants from freezing at relatively mild temperatures and reduce the frost injury.

We have had experiences in the field using more classically selected and constructed micro-organisms for such purposes, but in the last several months a colleague, Dr. Panopoulos, and myself at Berkeley have shown it possible that we can construct, using genetic engineering techniques, bacteria that we feel will be more effective in this biological control of frost injury.

The basic premise, then, is now that we have isolated the genetic material, the genes for ice nucleation, we can use this as a probe to specifically remove these genes from other micro-organisms in the field. We have had to go before the RAC committee to obtain permission to remove these genes from strains of bacteria found in the field.

Our concept, then, is to take micro-organisms that have evolved and are adapted for growth on healthy plants, only some of which might be potentially pathogenic to those plants; remove a single gene, making them unable to be detrimental to the plants in terms of causing frost injury. This, then, falls under the purview of genetic engineering, but the point that I would like to leave with you today is that we do not feel that this, what the terminology might call, deletion engineering is in itself inherently hazardous. We are dealing with micro-organisms which are already present in the environment, and we would simply be reintroducing these same micro-organisms, only slightly changed by recombinant DNA techniques, back into the environment. There we would hope they would compete in their natural habitat with the detrimental strains, those that still have these genes present.

Basically, then, we feel that this type of approach, not specifically relating only to the control of frost injury by the use of genetically engineered strains, but we feel another potential avenue, and one which will become more important in the future as well, will be that of control of other plant diseases. There are many important plant diseases that are caused by bacteria, as eventually with fungi as well, that we feel will be adequately controlled by a similar type of procedure.

We, therefore, feel that the release of such recombinant microorganisms which are already widely established and whose apparently only major environmental effect has been in causing of plant disease, or in this case frost injury, can be alleviated in a specific way by removing the genetic material involved.

Therefore, we would feel that these strains would not in themselves be any more harmful than the ones that are already present. Indeed, we feel they should probably be considered to be less hazardous than the original, but they would be debilitated in their ability to cause disease. In the case of our bacteria, they would be debilitated in their ability to cause ice formation. Because ice formation is involved in plant diseases, we feel it would also be considered to be debilitated in terms of plant disease initiation as well.

In summary, then, I would just like to throw this out as an example of deletion engineering, the removal of specific DNA sequences by recombinant techniques, which in our opinion should not be inherently hazardous. It would fall under the same purview as the regulation of the movement of strains now governed by USDA and APHIS. These strains should not be any more hazardous than the strains that are already present and should not offer any undue environmental impact.

Thank you.

[The prepared statement of Dr. Lindow follows:]

REPORT TO U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE AND TECHNOLOGY

Dr. Steven E. Lindow
Department of Plant Pathology
University of California, Berkeley

Biological Control Agents for Frost Injury of Plants

Bacterial Ice Nucleation and Frost Damage

Certain bacteria, such as Pseudomonas syringae van Hall (which includes various pathovars under the current taxonomic clarification), Erwinia herbicola Lohnis Dye, and, occasionally, isolates of Pseudomonas fluorescens Migula, cause nucleation of ice crystals in supercooled water at temperatures slightly below 0 C (threshold nucleation temperature about -1.5 C). Those bacteria are common plant inhabitants, existing as epiphytes in substantial numbers on above-ground healthy plant surfaces (leaves, twigs, buds, flowers). Large seasonal fluctuations from undetectable levels up to 10^7 cells/gram tissue fresh weight are often observed on plants. Some plants have many more ice nucleation active bacteria on their leaves than others. A causal relationship between frost damage on frost-sensitive crop plants at relatively warm subzero temperatures (down to -5 C) has been established. For instance, the degree of damage after exposure to low temperatures either in the field or in controlled environments (growth chambers) is directly related to the populations of ice nucleation active (INA+) bacteria present on the surfaces of above-ground parts. Plants grown aseptically can tolerate temperature of several (approx. 6) degrees Celsius below zero without apparent damage and they are rendered sensitive to such temperatures by spraying with suspensions of INA+ bacteria prior to low temperature exposures. Ice nucleation active bacteria have therefore been shown to be both necessary and sufficient to account for the frost sensitivity of many important agricultural crop plants.

Frost injury at temperatures above -5 C is a major problem affecting production of many important annual crop plants such as corn, soybeans, wheat, tomatoes, and other vegetables; deciduous fruit trees such as pear, almond, apple, cherry, etc.; and

1) Work reported and concepts discussed in cooperation with Dr. N. J. Panopoulos, C. Orser, and Dr. B. J. Staskawicz.

many subtropical plants such as citrus and avocado. Plant frost injury due to temperatures above -5 C (23 F) in the United States varies from year to year, but estimate of average annual losses range from one to three billion dollars. Worldwide agricultural losses are much higher. In addition to direct losses due to frost injury, many hundreds of millions of dollars are spent yearly in measures aimed at reducing mild frost injury. Methods such as the use of wind machines to mix warm air aloft with cold air near the ground, burning of fossil fuels to directly heat the air near crop plants, and pumping of large amounts of water to release the latent heat of fusion on or near crop plants are not highly effective and are costly and can reduce environmental quality. Therefore, alternative methods of frost control that could replace or supplement these methods are being sought.

One important new way to reduce frost damage to such plants is by reducing the natural epiphytic population of INA$^+$ bacteria on plants at the time of freezing temperatures. Significant protection against frost damage has thus been obtained by application of various bactericides, including antibiotics. The use of antagonistic bacterial strains which compete with members of the natural epiphytic flora has also been shown to be effective under field conditions and is the basis for this report. Antagonists especially suited for this purpose are INA$^-$ mutants of the naturally occuring INA$^+$ strains. These mutants, being basically adapted for epiphytic growth and survival, presumably displace their wild-type counterparts by occupying the same physical spaces (e.g., leaf-crevices, stomates, lenticels, etc.) and utilizing the same nutrients. Pilot experiments conducted both in the greenhouse and in the field with chemically induced INA$^-$ mutants of P. syringae and E. herbicola and plants such as corn, pear, almond and citrus, have demonstrated the effectiveness of this strategy under field conditions.

The gene(s) responsible for ice nucleation were recently cloned in our laboratories by constructing total genomic libraries from two strains of P. syringae pv. syringae and one strain of E. herbicola in E. coli HB101 and scoring for ice nucleation activity. Several Ina$^+$ recombinant colonies were thus identified. Recombinant plasmids from several of these were also introduced into INA$^-$ mutants of the DNA-source strains and complementation of the INA phenotype was observed. Extensive structural and functional analysis of one such plasmid from one P. syringae pv. syringae strain has been carried out to determine the size and location of the INA region on the DNA insert, and the presence and distribution of restriction endonuclease sites. Blot hybridization analysis has also been carried out to determine whether single or multiple copies of the INA region are present in the bacterial genome. Similar studies are underway with Ina$^+$ DNA inserts from the two other strains.

Our recent research goals have been to construct ina$^-$ deletion mutants of selected prototype strains of P. syringae pv. syringae and E. herbicola and evaluate their efficacy as biological competitors of epiphytic components of INA$^+$ populations occuring naturally. The advantages of such mutants constructed in vitro compared to chemically-induced equivalents are genetic stability and absence of silent mutations which may adversely affect competitive fitness. Should such constructed antagonistic bacteria prove successful in biological control of frost injury, many millions of dollars of lost productivity due to frost injury may be spared, millions of dollars in frost protection costs saved, and new options in plant varieties and agronomic procedures opened up due to a lowering of the inherent frost sensitivity of agricultural plants.

Although it is impossible to predict all safety and ecological impacts large scale releases of microorganisms might have, the deployment of deletion mutants of microorganisms to be re-released into their original habitat should pose the fewest risks. Since no additional phenotypic traits are being imported on microorganisms such as described above, they would be expected to be no more aggressive in their ecological niche than microorganisms with the original phenotype. Therefore, basic knowledge of the ecology and epidemiology of the original bacterial species should be required but should also be adequate for the safe deployment of modified strains. For example, knowledge of the following aspects of the biology and epidemiology of P. syringae and E. herbicola suggest that this would be suitable for deployment as described above.

Biology of Pseudomonas syringae

P. s. sryingae is an abbreviated taxonomic designation of Pseudomonas syringae pathovar syringae. This is the taxonomic designation currently accepted by the Judicial Committee of International Committee on Systematic Bacteriology (the "pathovar" system) and is synonymous with the earlier designation Pseudomonas syringae Van Hall. It is important to note, also, that a very large number of other plant pathogenic Pseudomonads distinct in their pathogenicity and biology from P. syringae pv. syringae are also classified as P. syringae in the current "pathovar" system but each has a different "pathovar" designation (e.g. P. syringae pv. phseolicola earlier known as P. phaseolicola) reflecting their pathogenic specialization.
Strains or isolates of P. s. syringae are reported to be pathogenic on many woody and herbaceous plants including bean, lima bean, wheat, barley, sorgum, corn, pear, apple,

plum, peach, cherry, citrus, and others. Some studies with isolates obtained either from disease lesions on herbaceous hosts or from epiphytic inoculum present on such hosts are restricted to a few hosts which are closely related. This is true, for example, for isolates infecting bean and stone fruits. Whereas these correlations are striking, other studies indicate less well defined host specialization (broader or overlapping host range for individual isolates). Thus, P. s. syringae is generally considered a less specialized pathogen by comparison with other plant pathogenic bacteria. However, there are several reasons to doubt many of the claims in the literature regarding its host range. For example, pathogenicity tests on host plants in addition to or including the host of origin were often conducted under conditions that were artificial and thus not representative of the true pathogenicity of these isolates.

Epiphytic biology

P. s. syringae is ubiquitous and colonizes the leaf surfaces of host and non-host plants in what has been called "resident phase". This is probably the major habitat for this species. According to several reports, isolates from resident phase populations are predominantly pathogenic on their epiphytic host and usually specific, with respect to pathogenicity, to that host. However, pathogenicity is not a prerequisite for epiphytic growth on herbaceous plants and any epiphytic advantage that a pathogenic isolate may have on a susceptible host is expressed over long periods of time as inoculum build-up rather than as specificity per se. It is possible that pathogenic capability of these strains also imparts upon them an advantage as epiphytes or that their epiphytic fitness is a significant component of their pathogenic host range under natural conditions. Due to their ice nucleating properties, epiphytic populations of P. s. syringae predispose frost-sensitive plants to freezing injury at relatively warm subzero temperatures.

Frost-conditional Virulence

Frost injury has often been reported as a predisposing factor for infection of some plants by P. s. syringae on several hosts (e.g. pear, apricot, peach). Ice formation is either required for or favors disease development in these cases. Most of those studies were conducted prior to the discovery of ice nucleation as a property of P. s. syringae or the availability of ice nucleation deficient mutants of the bacterium. The above evidence, although circumstantial, is highly suggestive that ice nucleation activity is a frost-conditional virulence determinant of P. s. syringae under field conditions. Therefore the Ina^- deletion mutants discussed here, in addition to being unable to cause frost injury are expected to be debilitated with respect to frost-conditional virulence.

Biology of Erwinia herbicola

Erwinia herbicola comprises yellow-pigmented bacteria commonly epiphytic on plants. Although it is commonly found in association with diseased tissue, it is mostly an opportunistic secondary organism. There are few documented instances of true plant pathogenicity of this bacterium, or its various synonyms, on tropical crops not grown in California or the mainland U.S. In other cases, it appears to effect a certain degree of biological protection against primary bacterial pathogens, such as *Erwinia amylovora* on pear.

There is some uncertainty regarding the possible relatedness of yellow-pigmented plant isolates classified as *E. herbicola* to similar isolates of clinical origin classified as *Enterobacter agglomerans*. To our knowledge, there are no reports of pathogenicity of plant isolates to man or animals or of clinical isolates to plants. Most isolates of *E. herbiola* of plant origin grow optimally at or near 28-30 C and only sparsely, if at all, at 37 C. This supports the prevailing view that pathogenicity of yellow-pigmented isolates classified as *Erwinia herbicola* or *Enterobacter agglomerans* to man or warm-blooded animals appears to be a property of isolates or clinical origin but of plant origin. Due to its ice nucleating properties, *E. herbicola* contribues to frost damage to plants.

In our opinion, the proposed release of antagonistic bacteria carrying deletion mutations does not pose significant risks to health or the environment. The arguments are the following:

1. *P. syringae* pv. *syringae* and *E. herbicola* are common and omnipresent plant epiphytes. *P. syringae* strains have also been widely distributed and applied to plants as a biological control agent of certain plant diseases.

2. Ice nucleation activity, in addition to causing frost damage, is considered to be a conditional frost-dependent virulence factor in *P. syringae* pv. *syringae*. For example, in spite of the fact that significant populations are present on plant surfaces, disease often occurs only after the ambient temperature drops to or below freezing. Presumably, localized frost injury results in the release of nutrients from damaged cells and water congestion of tissues which facilitates bacterial access to internal tissues. Accordingly, the INA$^-$ deletion mutants can be considered at least partially "debilitated" with respect to virulence.

3. E. herbicola is not pathogenic on plants. Frost damage, although injurious to plants, is not a disease in the classical sense.

4. For the above reason, it may be argued that our proposed experiments be restricted to E. herbicola. However, this bacterium is not an effective antagonist against P. syringae pv. syringae in planta because the habitats of the two differ, both in space and in time, although they partially overlap. (Note: the epiphytic population cycle of E. herbicola during the growing season differs from that of P. syringae pv. syringae.)

5. Previous studies with genetically marked strains have shown that, although the bacteria can be established on the phyllosphere of plants, they do not survive well through a full yearly cycle, i.e., their populations drop to very low levels during the dry season.

These epiphytic bacteria have been shown by other workers as well as us not to survive for more than a few days to a month in the soil. The bacteria can survive up to a year in plant debris on the surface of the soil, but die rapidly upon decay of the plant debris when incorporated into the soil. All plant debris in treated locations will likely be promptly incorporated into the soil upon completion of each growing season because of common agronomic procedures. Although some movement of bacteria to aerial sites near treatment locations by insect or aerial dispersal is possible, the numbers of viable cells transported has been shown to be very small and these cells are also subject to the biological and physical processes limiting survival as discussed previously.

6. All P. syringae strains proposed for use on a large scale would be isolated from the surfaces of healthy potato, tomato, pear, almond, and citrus plants. Although certain strains of P. syringae can be pathogenic to hosts such as pear, almond, and citrus, disease caused by this potential pathogen on these hosts is rare in California and occurs only after predisposition by freezing injury. Taken together, the use of avirulent strains discussed earlier, in the proposed location where these crops are absent, and on crops that are either nonsusceptible to the bacterium under California's climate during their growing season, offer effective safety to crop plants of the region. Because of the natural epiphytic ubiquity of P. syringae on both host and nonhost plants, the likelihood of increased disease on either homologous or heterologous plants by application of deletion mutants of P. syringae appears remote.

7. Previous field trials with these organisms assure us that no serious problems concerning safety of the bacteria to humans are likely to arise. Wild type strains of both bacteria have been sprayed on experimental plants in the field over a period of several years with no adverse effects on the individuals involved. P. syringae pv. syringae is not a human pathogen; indeed, it does not grow at temperatures above 33-34 C. Pathogenicity of E. herbicola on humans seems to be a property of strains of human, but not of plant origin. The strains to be used in these studies would originally be isolated from plants.

Biographical Sketch

S. E. Lindow

Present Postion:	Assistant Professor of Pathology and Assistant Plant Pathologist in the Agricultural Experiment Station Department of Plant Pathology University of California Berkeley, California 94720
Doctorate:	Ph.D., Plant Pathology University of Wisconsin, Madison, Wisconsin - 1977 Minor - Biochemistry
Thesis:	Leaf surface bacterial ice nuclei as incitants of frost damage to corn (Zea mays L.) and other plants.
Postdoctoral:	Department of Plant Pathology University of Wisconsin, Madison, 1977-1978
Bachelor's Degree:	B.S., Botany Oregon State University, Corvallis, Oregon - 1973
Citizenship:	United States. Born May 20, 1951, Portland, Oregon
Research Experience:	Ph.D. thesis and current and postdoctoral work on the ecology and physiology of ice nucleation active bacterial species.

Mr. GORE. Thank you very much.

Dr. Ralph Hardy is director of Life Sciences Research with Du Pont.

Welcome.

STATEMENT OF DR. RALPH W. F. HARDY, DIRECTOR OF LIFE SCIENCES, CENTRAL RESEARCH AND DEVELOPMENT DEPARTMENT, E. I. DU PONT DE NEMOURS & CO., WILMINGTON, DEL.

Dr. HARDY. Thank you, Mr. Chairman.

We appreciate the opportunity to comment in this hearing. I would like to comment on six areas briefly.

I will initially indicate Du Pont's involvement in biotechnology, our expectations from biotechnology; our pleasure at seeing the improved climate for agricultural research and the importance of that improved climate to building a strong agricultural biotechnology in the United States; what we perceive as the status and outlook for the science base that is key to a strong agricultural biotechnology; and from that science base, what is the status and outlook for crop production biotechnology techniques; look at the safety and environmental quality aspects; and, finally, comment briefly on some other concerns that we think are important for a strong agricultural science and biotechnology in the United States.

Let me begin by commenting from Du Pont's point of view on biotechnology. In 1979, we decided to establish a strong internal R&D program in biotechnology. We basically did that for four reasons. We felt that there would be major impacts of this technology on our life science-based businesses—diagnostics, pharmaceuticals, and agrichemicals. We also felt there would be impact on some of our commodity businesses, like the chemical feedstocks that go into polymer fibers, and so on.

We have stated that we plan to increase these businesses, which amount to sales of about $1½ billion on the life science side, aggressively over the next several years.

We also believe that the techniques of biotechnology are absolutely essential if you are going to do frontier research in the life science area, and that out of these may not come directly, but indirectly, products and processes of importance.

We felt we would be able to engineer cells that could produce products, like lymphokines, for example. In the longer term, we felt that we might be involved in engineering cells that are themselves products, like, for example, seeds, blood cell components, and so on.

In addition to the internal activity, we acquired New England Nuclear, which has strong capabilities in the monoclonal antibody area, to complement our techniques. We have also established relationships, to a modest extent, with universities like one for general expertise with Harvard and others with a few specific objectives.

At this stage we are pleased that we are seeing strong impacts of the still growing biotechnology program that we have on each of our business areas—diagnostics, pharmaceuticals, and agrichemicals.

Next let me look at the climate for agricultural research. In our view, we need a strong public sector if we are going to have a strong private sector component. We need this from both the training point of view and from the base of understanding aspects. That does exist in the United States in the health sciences area. That does not exist as well as we would like to see it in the agricultural area, but there have been a number of activities, governmental, scientific, et cetera, in the last year that suggest that, yes, that climate is improving and we are moving to build a stronger base in the agricultural research area.

If we look outside the country, we see organizations like the Commonwealth Scientific Industrial Research Organization in Australia, the Agricultural Research Council Plant Breeding Institute in the United Kingdom, each of which represents a larger, concentrated component of research going on in this area that underpins agricultural biotechnology than I think any single institution in the United States at this time has.

Let me move to the status and outlook in the agricultural science area. One establishes a base in science, and it is really from that base in science, then, that the technologies evolve.

In general, we are at the stage where science is much more evolved in the microorganismal area than the animal area. We heard about the super mice earlier this morning, and the animal area is certainly more evolved at this stage, more understood, than is the plant area.

There is a strong base, really, to do things in the microorganismal culture and genetics areas. We have heard examples previously on this panel of things that are occurring with potential in those fields.

If you go to the plant area, that is a more difficult area. The base that we have in the physiology and biochemistry of understanding the key processes in plants, processes like photosynthesis, the primary reaction that creates new biomass; or moving that material around, a phenomena called translocation; or reproductive growth; senescence; ion uptake; nitrogen fixation; and pest resistance is limited.

In general, we have a fairly inadequate understanding to build a strong biotechnology in the agricultural sciences.

Photosynthesis—in the last few years we have greatly expanded our understanding and some Achilles heels have been identified like, for example, the enzyme that fixes carbon dioxide and its nonspecificity whereby it fixes oxygen and makes agricultural crops, for the most part, substantially less productive than they would be. Does biotechnology hold a potential answer for this area?

Nitrogen fixation is another very visible field in this area. There our understanding has revealed that there are several Achilles heels—weaknesses in the biological nitrogen fixation system—one of them being, in fact, the large energy requirement.

The point here is that in our mind there are many processes that are key in agricultural crop productivity for which we do not yet have the basis for understanding. We need biotechnologies to improve them.

Plant molecular genetics is very early. At this stage we maybe know about 25 of the 100,000 or so genes of any one plant. Within the last year a foreign gene has been transferred into a plant and made to function. This is certainly a milestone event. It is not a practically useful one. One might expect in the next year or two that we will see genes with agronomic utility beginning to be transferred.

Regulation of plant gene function—not all of these genes are turned on at any one time, and it is key I think that we understand what turns genes on and what turns genes off, so that we can selectively cause those to be turned on that we want and those to be turned off that we do not want turned on at a particular time.

In time in this science I think we will come to gene design. Genes have certainly some weaknesses in them for agricultural purposes, and we have seen within the last year the first examples of designing genes based on the knowledge of how they function to make them function in a somewhat different way.

There are many things to do, and that need to be done in the plant science area.

Where are we in the biotechnology area and in agriculture? Crop productivity over the last several years worldwide has increased at something like 2 to 3 percent per year. This strong increase then in crop productivity was brought along by plant breeding and plant protectants—fertilizers, irrigation, mechanization, and so on.

If we look at world growth population—up to maybe 6 billion people by the end of this century—and if we look at the need that this will create—a need for nutritious and inexpensive domestic food, the export demand need that will occur, and the need to feed the hungry—probably our old technologies will not be enough. They will need to be supplemented. Certainly, genetically engineered crops, a direct potential product of biotechnology, and plant growth regulators, agents to increase the yield of nutritious crops, could be important products. In fact, plant growth regulators, some envision, may have as large a market as do plant protectants at the moment, which is something like $15 billion worldwide.

Biotechnology, then, we think can contribute to both of these.

As we look at where we are in the sequence of things in the plant tissue culture area we have found that you can increase genetic diversity as you culture crops. This is not recombinant DNA, but simply passing cells of plants through tissue culture. This has been effective in sugarcane. It is out in the field and being used. It is being looked at in major crops such as wheat and potatoes. Here is a major opportunity that is now at the stage of being applied.

DNA probes to detect disease organisms and facilitate plant breeding, are now starting to be utilized.

The ability to transfer single genes has been demonstrated in the past year, and one will see in the not distant future storage proteins with improved nutritional qualities, herbicidal resistance genes, and so on, being transferred and expressed in crop plants.

Multiple gene transfers may be required to get stable disease resistance. That is going to be a more complex problem in terms of identification of the genes, transfer of the genes, and so on, but undoubtedly in the next few years that capability will be achieved.

In the longer term, we will probably be giving plants new capabilities that they do not now have. In that category I put the area of nitrogen fixation. This is a fairly formidible task in our judgment because there are several genes involved. It is a very energy-consumptive process. Moreover, the enzymes that are the products of that gene are, in fact, extremely sensitive to oxygen in the atmosphere.

At this stage I think it is question mark on what will be the economic benefit. A self-fertilizing crop for high production agriculture.

If I look a little farther down the road, I think the day of scientist-designed genes will come. For example, the carbon dioxide fixing enzyme may be an area where this type of technology, biotechnology, will be applied. From field tests at this stage, one knows that the opportunity should be quite large in that area. If you experimentally correct a deficiency in that enzyme, not a practical correction but experimentally, you see up to a 100-percent yield increase in soybeans. Therefore, it is a major opportunity without additional inputs in terms of crop productivity.

Also, I think you will see agrichemical regulators coming out of this, chemical molecules which will specifically turn on or turn off, (regulate) genes so that you have them functioning at the time that you want them to function. There is clearly, then, a bright opportunity but we are very early, in our judgment, in biotechnology as it applies to agriculture.

Let me comment on safety and environmental quality. In general, we support a controlled, stepwise, progressive program of development beginning in the laboratory, moving with deliberate caution through the plant growth room and greenhouse before finally entering limited field evaluations which can be closely supervised. We think this is consistent with the progression that has occurred in the NIH guidelines from a very cautious approach initially. As one found that, in fact, the potential hazard was small or negligible, that very cautious approach was moved to a more liberal one. We think we should proceed in the same way in moving material into the environment.

In the agricultural field, we do not see health hazards to personnel, certainly that have been involved at this stage.

The release of plants into the environment going through the stepwise approach that I mentioned previously, if there is a problem that develops, there is a reasonable recall for plants. That reasonable recall is very effective herbicides. Limited field testing could accomplish that.

I would argue probably in the kudzu case that had we gone through limited field trials and found the problem that has evolved there, that herbicides could have been a quite effective recall for that material. That is the situation as we see it in plants.

In micro-organisms we think that should be a more cautious approach. The reason for that is micro-organisms are more difficult to recall after they are out in the environment than are plant species. Also, certain aspects of the microorganism area might cause us even to be more cautious in these cases. The ones I am referring to are areas where we may be creating microorganisms that are new symbionts. The line between a new symbiotic microorganism and a pathogenic species—and I refer to the example of *Rhizobium*, a useful species, a symbiotic species in nitrogen fixation, and a pathogen *Agrobacterium*—is a fairly small one genetically. I think our major concern here should be, if we create new symbionts, that we check carefully that they do not revert and become pathogenic before we move them out of the growth room and greenhouse into a less recallable situation.

We support the NIH guidelines at the moment. We think they, plus other existing legislation that has been talked about already, are in fact adequate to cover this area. The combination of the Institutional Biosafety Committee and the RAC subcommittees is adequate to examine release into the environment.

Finally, some other concerns for a strong agricultural biotechnology:

We feel that there does need to be expanded support for public sector plant science, that the base of information needs to be expanded, that the training of people in this area needs to be expanded, that we do have a deficiency of plant-trained biotechnologists. We support the novel funding program that the National Science Foundation started this year in terms of providing special funds for people outside of agriculture to come in and be trained in the agricultural area.

We also note that we would not like to see an expansion of basic science at the expense of existing plant production research, which is very critical to both growers and certain segments of industry.

We also note in the Government-university-industry interactions area that we would like to see these become more interactive. We see tests in the university-industry relationship scene at the moment, and I think we need to be careful not to adulterate, if you will, the role of our universities. They are information generators and trainers and should not become overly concerned with the commercial input.

The strength and duration of proprietariness is an area that applies here. Many of the products of this area will require demonstration of safety, and will require demonstration of efficacy. That will take probably a considerable time. To have industry maximally contributing in this area, the patent term restoration legislation could be the very key to this area.

In conclusion, then, let me say that the agricultural biotechnology research is moving at a rapid pace. There are new, exciting, practical applications that are just beginning to emerge. The field has immense potential to benefit mankind. It is relatively low risk for the personnel involved and for the environment. Adequate controls and safeguards are provided, in our judgment, through existing guidelines and administrative regulations.

We must foster an advancement of agricultural biotechnology through training a cadre of new scientists in our universities and by providing incentive for industry to bring the results of the basic scientific discoveries to practical application.

[The prepared statement of Dr. Hardy follows:]

Statement of Dr. Ralph W. F. Hardy
Director of Life Sciences
Central Research & Development Department
E. I. du Pont de Nemours & Company
June 22, 1983

Before The

U. S. House of Representatives Science and Technology
Subcommittee on Investigations and Oversight
and
Subcommittee on Science, Research and Technology

INTRODUCTION

Good Morning, I am Ralph Hardy, Director of Life Sciences in the Central Research & Development Department of the Du Pont Company. I am also a member of the Executive Committee of the Board of Agriculture of the National Research Council and a member of COGENE, which is the Committee on Genetic Experimentation of the International Council of Scientific Unions. I appreciate this opportunity to provide comments on biotechnology for agriculture. I will address the following: (1) Du Pont's involvement in biotechnology and our expectations; (2) evidence for improvement in the climate for agriculture research as it relates to biotechnology and the need to further strengthen U. S. public sector agricultural research and training; (3) status and outlook for the science base for agricultural biotechnology; (4) status and outlook for plant production biotechnologies; (5) agricultural biotechnology and safety and environmental quality, and (6) other concerns relevant to assuring a strong agricultural science and biotechnology.

Du Pont and Biotechnology

In 1979, we at Du Pont decided to establish a strong internal R&D program in the new biotechnology. We made this decision for four reasons. We expected the new biotechnology to make a significant impact in our current and future life science based businesses-diagnostics, pharmaceuticals and agrichemicals and our commodity chemical businesses--chemical feedstocks. We have stated that we plan to increase substantially our life sciences-based businesses from their current $1.5 billion sales. We recognized that the techniques of biotechnology were essential for research in any life science area and that the understanding from use of these techniques indirectly would lead to major new products and processes. We expected to engineer cells that would produce products and we also, in the longer term, expected to engineer cells that would themselves be products. We have supplemented our internal R&D with the acquisition of New England Nuclear with strengths in monoclonal antibodies, one of the key new techniques of biotechnology. We have established a few relationships with universities such as one with Harvard for general expertise in this area and others for specific scientific objectives. We are pleased that we are seeing strong impacts of our still growing biotechnology programs on each of our diagnostic, pharmaceuticals and agrichemicals areas.

Climate for Agricultural Research

A strong public sector research program is essential for private sector success in developing significant new products and processes. The public sector provides trained scientists and a base of understanding from which the private sector develops, manufacturers, and markets products and processes. The U. S. public sector base in the health sciences is strong and we in Du Pont, are encouraged by evidence that suggests improvement in the climate for public sector agricultural research. For instance, in the 1982-83 period, U. S. agricultural research overview activities increased. The Office of Technology Assessment (OTA) issued a critique and prepared options for the U. S. agricultural research system. The White House Office of Science and Technology Policy (OSTP) and the Rockefeller Foundation sponsored a meeting at Winrock which produced recommendations on "streamlining" agricultural research. Agricultural research was one of seven areas selected for which the Committee on Science and Engineering for Public Policy (COSEPUP) of the National Academy of Sciences/National Academy of Engineering and Institute of Medicine produced a briefing report for the OSTP to support budgeting of additional funds in fiscal 1984. A Board on Agriculture was established by the National Research Council with, for the first time, equivalency to its other boards and commissions.

Scientific meetings and publications in 1982-1983 have also focused strongly on agriculture. The U.K. Ciba Foundation, which has held several hundred meetings on health science convened its first meeting on agriculture entitled Better Crops for Better Foods and plans to hold additional meetings in related areas. The second world meeting on chemical research applied to world needs (CHEMRAWN II) held in Manila, focused on new research frontiers of chemistry and world food supplies. The 15th Miami Winter Symposium, an annual meeting on the science underpinning biotechnology was devoted, for the first time, exclusively to agriculture. A meeting on Agriculture in the Twenty-First Century was held this past April in Richmond under the sponsorship of Phillip Morris. The National Academy of Science sponsored a "Convocation on Genetic Engineering of Plants: Agricultural Research Opportunities" in May. All of these support the growing interest and recognition of agriculture research in the academic, government, and private sectors.

Established agricultural research organizations are also expanding their efforts. We estimate that U. S. agricultural research and development expenditures were over $5 billion in 1982 with slightly more than half spent by the private sector. The traditional research organizations in the U. S. are the Agricultural Research Service, the state universities, the agricultural experiment stations, the private foundations, and companies involved with agricultural chemicals, veterinary products, seeds, farm equipment, food and feed products, and forest and forestry products. The dawning of the era of the new biotechnology is causing a number of these traditional research practitioners to expand their activities. For example, the state of New York identified Cornell University as a Center of Excellence in Biotechnology for Agriculture. Other states have also focused on the biotechnologies.

Several major industrial organizations, including my own at Du Pont, as noted above have established major in-house research programs in biotechnology as it relates to agriculture. In addition, several smaller speciality companies have been formed to pursue biotechnology applications in the agricultural marketplace. Moreover, major private universities such as Harvard, the University of Pennsylvania, Rockefeller University, Washington University, and Stanford University have become strong contributors to fundamental knowledge relevant to agricultural biotechnology. In the international community, there are some strong centers of research relevant to agricultural biotechnology such as the U. K. Agricultural Research Council's Plant Breeding Institute and the Australian CSIRO's Plant Industry Division. The U. S. has no single public sector research center focused on agricultural biotechnology as large as either of the two above mentioned centers.

Status and Outlook for Agricultural Science

A number of sciences are key to developing biotechnology for plants. A few are in hand, many are being explored and some are yet to be explored. Microorganismal culture and genetic techniques are for the most part in hand. The molecular genetics of microorganisms is highly developed, that of animals somewhat developed and that of plants is very early in development. Plant cell and tissue culture technologies including regeneration of mature plants is established for a few plants but has yet to be developed for most crop plants. The general techniques of making monoclonal antibodies are equally applicable to plants as to animals and microorganisms.

The physiology and biochemistry of key plant processes, e.g., photosynthesis, translocation, reproductive growth, senescence, ion uptake, N_2 fixation and pest resistance are inadequately known in most cases and this understanding limitation may be a major barrier to realizing the potential of biotechnology in crop production agriculture. During the last decade our knowledge of the biochemistry of photosynthesis, the primary reaction that creates the biomass on which all life depends has progressed rapidly and revealed a major limit to crop productivity. Nature's gene for photosynthesis, the CO_2-fixing gene, makes an enzyme that fixes CO_2 but is inadequately specific and fixes O_2 in a non-useful and in fact wasteful reaction for crop production. Can biotechnology find ways to eliminate this undesirable O_2 reaction and thereby increase agricultural crop productivity? During the last two decades the knowledge of the biochemistry of N_2 fixation has made rapid progress and revealed that this key biological reaction has many undesirable characteristics that limit its application in production agriculture. In this case an excessive energy requirement is one of the major problems. Undoubtedly increased understanding of other key plant processes will reveal limitations and thereby opportunities for improvement.

We are very pleased that plant molecular genetics has advanced in recent years, but our understanding of plant molecular genetics is still very early with possibly twenty-five of the hundred thousand genes in a plant cell characterized. However, in the last few months, a system to transfer a functioning foreign gene into a plant cell has been demonstrated--plant cell gene transfer is now where animal cell gene transfer was a few years ago. The major almost unexplored science area in plants is understanding the regulation of the functioning of plant genes. This most important area will reveal what turns plant genes on and what turns them off. At any one time only a small fraction will be turned on. What are the controls? Such understanding will be most useful. Finally, the science of gene design by combining the frontiers of chemistry and biotechnology has been demonstrated during the past year and should enable us to accelerate change so as to improve plants for agricultural purposes.

Status and Outlook for Agricultural Biotechnology

Knowledge gained through agricultural research programs has and will provide the basis for new and improved applied technology. Crop production has increased at about 3% annually during the last few decades driven by the technologies of traditional plant breeding, fertilizers, plant protectant chemicals, irrigation and mechanization. World population is projected to grow from the present about four billion to about six billion by 2000 A.D. In order to meet this long term challenge of a nutritious, inexpensive domestic food supply and at the same time meet the world export demand and needs of the hungry, a combination of the above existing and new technologies will be required. We judge that biotechnology will be essential to these new technologies. Specifically, we see these new technologies as genetically engineered crops and plant growth regulators. Biotechnology will directly contribute to genetically engineered crops as outlined below. Biotechnology, through understanding generated by it, will contribute indirectly to the discovery of plant growth regulators. Plant growth regulators are expected to enhance yield, improve nutritional quality and facilitate harvesting operations.

Let me now expand on the status and outlook for biotechnology in plant production agriculture. The popular expectations are self-fertilizing plants and plants resistant to biological and physical stress. Most of these expectations probably will not be realized until the distant future. Others are being realized or should be in a short time. Innoculation of legumes with Rhizobium microorganisms is a well established technology to enable legumes to fix their own nitrogen. Soil innoculation with Mycorrhizal microorganisms is now being used to facilitate nutrient uptake by plants. These nutrient input technologies should be improved by the new biotechnology. The genetic diversity of plants appears to increase when cells of the plant are cultured and the whole plant regrown therefrom. Scientists have called this technique somaclonal variation. This technique of increasing genetic diversity has been useful for sugarcane and some other plants and is now being explored as a biotechnology breeding technique for crops such as wheat and potatoes. Another biotechnology technique using a piece of DNA detects latent disease organisms in plant breeding material thereby greatly facilitating the time required to select disease-free stocks for conventional plant breeding.

Within the near term agronomic traits that rely on a single gene will be transferred to crop plants. Examples of such genes may include those for storage proteins with improved nutritional qualitites or those for herbicide resistance. The latter case may lead to herbicide-crop cultivar genetically matched couples. In the more distant future agronomic traits that require multiple genes will be transferred to crop plants. Examples include stable disease resistance which is believed to require multiple genes. Other examples include those genes involved with yield none of which are yet identified. In time crops will be given totally new capabilities such as the ability to fix their own nitrogen, the much publicized self-fertilizing corn. This self-fertilizing capability is probably one of the more difficult applications of agricultural biotechnology since it involves several genes, excessive energy requirement by the enzyme, and a need for the enzyme to be compartmentalized so as to almost completely exclude oxygen. The economic benefit of self-fertilizing corn is not clear. In the longer term scientist designed genes will become important such as a CO_2-fixing enzyme that does not react with O_2 in a wasteful reaction--the impact of such a designed gene could produce huge improvements in the yield of most crop plants with little need for additional inputs. For example, in field experiments where we have eliminated the wasteful O_2 reaction by aerial CO_2 enrichment, major yield increases were produced. In the case of soybean, the yield increase approached 100%.

We also envision that as we understand more about the regulation and coordination of gene expression in plants (which are processes that control plant growth and development), we will design and use chemicals to selectively turn on or turn off genes at critical stages in order to effect beneficial changes in plant growth, development, metabolism, and pest resistance. Such agrichemicals could be a major indirect impact of biotechnology.

Safety and Environmental Quality

Exciting as the advances which may be realized through biotechnology may be, we must also be congnizant of some potential safety and environmental quality concerns which could result from the application of these developing technologies. In order to assure that any potential hazards do not become reality, we recommend a controlled, stepwise, progressive program of development beginning in the laboratory and moving with deliberate caution through the plant growth room and greenhouse before finally entering limited field evaluations which can be closely supervised. Through such a programmed cautionary approach, we can maximize the scientific impacts while minimizing any untoward consequences for the environment. This stepwise approach is consistent with the NIH guidelines which were initially quite cautious and were revised to be consistent with experience.

At this time no health hazards have been identified for personnel involved with biotechnology research, scale-up or development in the plant sciences. With plant research involving recombinant DNA techniques carried out under the NIH guidelines we feel that adequate standards of safety can be maintained for the worker.

The original concerns voiced about recombinant DNA research were based on projected consequences of release of new organisms into the environment. These include the potential for release of new plant pests which might cause devastation to agronomically important species. Such organisms could be plant or microorganism species which might find an ecological niche and be difficult to control. By using the controlled developmental approach outlined above, and operating under the NIH guidelines established for recombinant DNA research, such deleterious consequences should be avoided. As an example, if a new potentially useful plant species were developed in the laboratory but subsequently found to be a potential pest such as a weed when released into a specific environmental situation adequate control measures such as herbicides are available to destroy the new species so that it would not gain an uncontrolled foothold and adversely affect the ecosystem. Such early recognition, planning and control would avoid environmental consequences such as those now being realized as a result of the introduction of the kudzu vine for erosion control in the Southeastern U.S.

With the development of novel microorganisms through the application of the techniques of molecular genetics a more cautious approach may be necessary since it is more difficult to recall or control microorganisms than plants. The line that distinguishes symbiosis, a beneficial relationship, from pathogenesis is indeed fine. This is evidenced by the genetic similarity between the Agrobacterium (a tumor-forming pathogen) and Rhizobium (a mitrogen-fixing bacteria which forms a symbiotic relationship with legumes such as soybeans). Therefore, means must be established to assure that a new organism created to aid agricultural production such as through the symbiotic fixation of nitrogen in monocytoledonous plants or enhanced utilization of plant nutrients from poor soils does not convert to a pathogenic form. This will require extended periods of laboratory, growth room, and greenhouse testing under varying simulated environmental conditions prior to actual field testing. Such a controlled approach to beneficial applications of the results of new recombinant DNA technology can be adequately covered through the existing oversight mechanisms contained in the NIH guidelines. We support the NIH Recombinant DNA Advisory Committee's (RAC) position with review by the local Institutional Biosafety Committee and a Subcommittee of the RAC.

Other Concerns

I would like to turn now to some other concerns related to agricultural biotechnology research and technology.

As noted earlier we need to expand support for public sector plant science research-government and university laboratories. This expanded research will fuel biotechnology with the necessary enlarged base of understanding and will train plant biotechnologists where there is a major current deficiency. Novel funding programs should attract talent to be trained in agricultural biotechnology. The special agricultural fellowships initiated by NSF this year are an attractive approach to meet this need. It is important that the expansion of fundamental agricultural science not be done at the expense of existing plant production research which is judged to be useful to growers and industry. Additional support funds rather than reallocation may be necessary. In "streamlining" our agricultural R&D system it is critical that we retain the useful parts and supplement them with needed fundamental sciences.

We need to seek ways for effective government/ university/industry interactions. Various university/industry relationships are being tried. These relationships should not adulterate the major role of either partner. We should expect our universities to train the leaders of tomorrow and to expand the frontiers of knowledge without excessive short term commercial focus. It may be of some concern that many of our leading university plant biotechnologists have equity relationships with small specialty biotechnolgy companies. This possible concern will disappear undoubtedly as these new companies evolve.

Adequate strength and duration of proprietariness is essential for the private sector to obtain a reasonable return on investment in biotechnology. Many products of biotechnology in the agricultural and health care area will require demonstration of safety and/or efficacy prior to marketing. This may require several years. Extension of patent life to make up for the years required to meet regulatory requirements will encourage vigorous commercial searching and development of biotechnology products by U. S. industry. We support Patent Term Restoration legislation which answers the above conerns.

In conclusion, let me say that biotechnology research is moving at a rapid pace with new exciting practical applications beginning to emerge. This field has immense potential to benefit mankind. It is relatively low risk for those directly involved in the scientifc efforts, for the general population, and for the environment. Adequate controls and safeguards are provided through existing guidelines and administrative regulations. We must foster advancement of biotechnolgy through training a cadre of new scientists in our universites and by providing incentives for industry to bring the results of the basic scientific discoveries to practical application.

RALPH W. F. HARDY

Ralph W. F. Hardy is Director - Life Sciences in the Central Research & Development Department of the Du Pont Company. Previous positions include Assistant Professor of Biochemistry at the University of Guelph, Ontario, Canada (1960-63), Research Biochemist, Du Pont (1963-67), Research Supervisor (1967-74), Associate Director (1974-79), and Director - Life Sciences (1979-present).

A native of Lindsay, Ontario, Canada, where he was born July 27, 1934, Dr. Hardy received his B.S.A. in chemistry in 1956 from the Ontario Agricultural College of the University of Toronto and was awarded the Governor-General's Silver Medal. From the University of Wisconsin, where he was a Wisconsin Alumni Research Foundation Fellow and a Du Pont Fellow, he received the M.S. degree in 1958 and the Ph.D. degree in 1960, both degrees in biochemistry.

Dr. Hardy is a member of the Board on Agriculture of the National Research Council and COGENE (Committee on Genetic Experimentation) of the International Council of Scientific Unions. He is on the editorial boards of Plant Physiology, Plant Cell Reports, Plant Growth and Regulation, and Biotechnology Patent Digest. He was a member of several national and international committees on world crop production including the National Academy of Sciences World Food and Nutrition Study. He is the editor of the three volume comprehensive "Treatise on Dinitrogen Fixation" and coauthor of a monograph "Nitrogen Fixation in Bacteria and Higher Plants."

Mr. **Gore**. Thank you very much. This is another very interesting panel.

I was encouraged by your statement, Dr. Hardy, that you think you can have limited field evaluations that are closely supervised where these new, larger organisms are concerned.

However, then you say that extra care and more caution are appropriate where micro-organisms are involved, but you say that, even there, you feel somewhat confident that procedures can be devised to field test new organisms in a way that answers many of the concerns that are implicit in this hearing.

Is that your view?

Dr. **Hardy**. Yes, that summarizes our position. In the plant area, clearly one can recall. At the same time, we think you should go through steps of growth rooms which are very well-contained laboratories and can be made as high contained as laboratories that were used earlier in recombinant DNA.

Move from there to a greenhouse, which is a reasonably controlled situation. Move from there to a limited field trial situation.

If one finds problems in terms of overcompetitiveness at that stage, then there are agents available to recall that experiment.

In the bacteria case, it is a little bit more difficult in terms of recall. We are suggesting that it be a more cautious experimentation as you go through the growth room and the greenhouse situation before you go into the field situation.

Mr. **Gore**. Let me ask you, Dr. Chakrabarty, how would you envision a field test of your oil-eating bug, for example? How could you be certain that it was recalled if it failed the test?

Dr. **Chakrabarty**. Mr. Chairman, in the case of the oil-eating bug, for example, I would really like to talk more about the pollution-eating bugs because I think we have a bigger chance of immediately applying these bugs than the oil-eating bugs, but I will just——

Mr. **Gore**. Let's talk about either one.

Dr. **Chakrabarty**. OK. Let me talk about the pollution-eating bug because there are all kinds of apprehensions about oil-eating bugs, and so on.

Pollution, of course, is a real problem, as you know, Mr. Chairman. We think that it could be possible for us to actually develop micro-organisms that do not exist in nature yet that would be able to eat many of the highly toxic pollutants.

The way we do it, Mr. Chairman, is that we take a natural micro-organism, micro-organisms that exist in nature, and we simply modify them genetically so that they can do just one thing, which is to eat the toxicants.

We feel that there is no other change to the micro-organism that you can detect. We feel that because it is a pure culture you can do extensive toxicological and other tests to make sure that it does not cause all the toxicological problems. Then my argument is that because it is a naturally occurring micro-organism, because the only thing it does is just eat a toxic chemical with complete mineralization, so that it does not leave anything behind, and because we actually added at the level of, let's say, 0.1 to 1 percent of the total microbial load of the soil, we feel confident that there will be no problem in terms of any kind of hazard that we can foresee.

However, as you correctly point out, there are really no defined guidelines that will allow me to go and do just that. In a sense, that is why I am here—to appeal to you to come up with appropriately defined guidelines that will allow me to not only develop micro-organisms, but actually do field tests with them, so that I can prove, once and for all, whether they will be effective in actually cleaning up the toxic chemicals.

Mr. **Gore**. We hope to address that problem in the report of this subcommittee's hearing.

Mr. Walgren?

Mr. **Walgren**. Thank you, Mr. Chairman.

When we talk about wanting to have these guidelines, is it a problem in your estimation that they remain only guidelines; that as guidelines they are not mandatory? Of course, being satisfied that there are not unusual risks or that you are satisfied that it only does this and nothing more is always in the eye of the beholder, and the beholder in those circumstances may have a very immediate benefit from getting it out there or getting it into that stage, a financial benefit.

Must we have more than guidelines?

Dr. **Chakrabarty**. That is a very good question, Mr. Chairman.

The way I see it, we can proceed in either of two directions. We can make very restrictive legislation and then operate under those circumstances and gradually find out that such micro-organisms really do not cause any problem, and then get legislation to relax them, or whatever. That is one alternative.

The other alternative that we are suggesting is that let's start by defined guidelines. As I said, the reason for that is that I do not really anticipate any kind of problem, because if you look back and see why the guidelines came up in the first place. I think a lot of people were concerned because we were really talking about cloning eukaryotic DNA into micro-organisms. We were not really concerned in terms of manipulating microbial genes. We have been manipulating genes in micro-organisms for years. What we were really concerned about is the fact that for the first time we learned how to introduce eukaryotic DNA in micro-organisms so that the micro-organisms would produce all kinds of exotic products, products that really are made within our body, in very stringent amounts. Of course, if the micro-organisms get in there and start producing those highly biologically active products in large amounts, you might encounter problems.

Mr. **Walgren**. Let me ask you this: Du Pont says that it follows the NIH guidelines voluntarily. What should the penalty be if they did not follow the NIH-defined guidelines in your terms?

Dr. **Chakrabarty**. I am not sure there should be a penalty unless you can prove that something—that they did something illegal or unethical or immoral. That is the point I am trying to make—that if the micro-organism produces something that poses some kind of a danger to the human beings, obviously there should be legislation, guidelines, whatever you want to come up with.

What I am arguing is that the kind of micro-organisms I am talking about, and most of us are talking about, micro-organisms that can do just one thing—eat up a chemical in its entirety so that nothing is left behind. In that sense, there is nothing but really a modified natural micro-organism. I do not see any potential hazard. Therefore, I do not want to start out with highly restrictive legislation, only to gradually get rid of it on time.

Mr. **Walgren**. However, you are not sure enough of the lack of potential damage to not ask for limitations on liability for a field trial. You feel that that is a necessity.

Dr. **Chakrabarty**. That is because it is a real-world situation. I do not exactly know why General Electric did not commercialize, but I heard the rumors since I left GE that one of the problems in using any kind of micro-organism that has been untested is to get appropriate insurance coverage. You do not want to introduce something new, only to be sued by various people.

Particularly if we really want to get rid of the dioxins from the environment—let's take that for an example. Let's say that I develop a bug that I find in the lab to be very effective in removing dioxin. How do I really go and appeal either to the Environmental Protection Agency, or whoever, to let me use it? Of course, I do not think they can really let me use it unless I satisfy them if anything goes wrong that appropriate care would be taken to satisfy the need of the affected people.

I do not ask for limited liability because I really think that there is any danger. It is just that in order to be pragmatic about it I need insurance to cover myself, and I cannot get insurance without limitation of liability because insurance companies seldom know anything about micro-organisms. They get extremely scared once they hear of genetically engineered micro-organisms.

All I want is some kind of defined guidelines to actually allow me to go and test some of the micro-organisms that I develop. I think limited liability is one of the necessities.

Mr. **Walgren**. May I ask Dr. Hardy to comment on this guideline and how mandatory should the guidelines be?

Dr. **Hardy**. Yes. I would like to make a couple comments.

I think if we look at the history of the NIH guidelines, they have worked admirably well in what we set out to achieve. One was concerned about a hazard. We made quite restrictive guidelines. Those changed, and changed fairly rapidly, in response to the hazard not being near what one perceived it to be.

Experiments were done and we saw we should not be as concerned as we were.

I would doubt that if we had legislation that the legislation would be as fluid as to change as rapidly as the experimental results.

Mr. **Walgren**. What about legislation making fluid guidelines mandatory?

Dr. **Hardy**. Then there would not be any fluidity to the guidelines. If you look over the history of the last 6 or so years that the guidelines have been in existence, they have changed pretty dramatically in response to the information that has been developed.

The strength that we have, I think, in the area of biotechnology in the United States at this stage is in part due to the fact that those guidelines did change and the experimentation was possible and could be pursued fairly aggressively.

I think we would severely delay agricultural biotechnology development if we put in place legislation. It is reasonable that we think about what should be the guidelines in terms of release into the environment.

In Dr. Lindow's area, the Federal Register of June 1, volume 48, No. 106, page 24549, refers to his specific case. There it says:

> Prior to the field applications of these materials, the investigators plan to test the mutant strains in a contained environment, such as growth chambers and greenhouses, to verify that they do not induce frost or other injury to plants and that they are capable of colonizing leaves.

That, to me, is proceeding in a deliberate and stepwise manner. Maybe we need some more of that expanded in terms of guidelines for release of different sorts of organisms into the environment—plants versus bacteria, et cetera.

Mr. Walgren. However, is it true that the only reason Dr. Lindow's proposal is in the Federal Register is that there must be some funding coming from a Federal research source, and that if he were a totally private entity, he could be proceeding as rapidly as he would like?

Dr. Hardy. We have two Institutional Biosafety Committees in Du Pont, one for the Wilmington part of the corporation and one for New England Nuclear that is located in the Boston area. A proposal to do this sort of thing would come to our IBC, and in my judgment would then proceed to the RAC before we would proceed.

We tend to be very, very cautious in taking new steps down the road. It would be a grave mistake, I think, at this stage if anyone were to proceed to aggressively and make a significant mistake in this area. That would create a lot of damage for the development of this area.

If we are going to err, our position would be we would want to err on the cautious side.

Industries that I am familiar with I think would go down that same road.

Mr. Gore. Would my colleague yield?

It seems to me the real question is where the burden of proof is going to lie. We cannot just take your word, Dr. Chakrabarty, as the originator of an organism that everything is safe. Despite all our expertise, there may be some ecological consequences that you have not foreseen. When those consequences are reviewed in the current government setup, the ecological consequences are really not considered. RAC does not have any ecological—any ecologists on it. They do not look at that aspect of it.

Mr. Karny pointed out in his testimony that they have on occasion expressed the need for some expertise in that area. Now when we get ready for the deliberate introduction of new entities into the environment, it seems to me that the burden of proof should be on the originators of these new entities to tell us that they are going to be safe. Now that burden should not be so onerous as to prevent the development and introduction of these entities. There is no real disagreement about that. I think the range of difference here is not very great, but we do need to find some way to address these problems and make certain that the originators of these new entities do carry that burden of proof.

When you say that the insurance industry just does not understand your business, government has experienced situations in the past where the promoters of a particular technology have said that the insurance industry just does not understand and we need to have a legal limitation, and later on it has appeared that the insurance industry might have had some reasons for its nervousness and squeamishness.

In this case if the insurance industry is unwilling to insure you, then I am not sure that we ought to shift the burden of proof to the public and to the ecology by saying, "We're going to take the word of the originator that, based upon his understanding of this stuff, it does not seem to pose any problem."

Does that sound unreasonable to you, Dr. Chakrabarty?

Dr. CHAKRABARTY. No. I think, Mr. Chairman, that you are absolutely right. I think you were exactly right when you said that there should be an ecologist on the RAC panel. I have no quarrel with that.

The only point I am trying to make is that, as you just said, Mr. Chairman, the regulations should not be so onerous so that, unless we have an ecologist on the RAC panel and unless we can foresee how a particular field trial is going to affect the ecology, that we should not do the field trial at all. After all, we do this in response to specific problems.

The question is really a difficult question because in many cases you cannot really predict how a field trial of a particularly genetically modified bug will actually affect the ecology. It is very difficult to predict. The question I am asking is, do I need to answer that first without really having any kind of understanding as to how it could affect the ecology or do I get some kind of a go-ahead, so that I can use the micro-organism, make sure that I can get rid of a particular problem, be it dioxin or whatever, and if there is any problem, let's be more careful about that in the future.

Mr. GORE. Suppose it is too late.

Dr. CHAKRABARTY. That is why I am advocating the presense of ecologists on the panel that sets up the guidelines, because they should be able to foresee as much as they can as to what might be in the offing.

The question is—after all, the purpose of all—it is particularly true, Mr. Chairman, in the case of pollution. You have to realize that there is no money to be made. It is basically for a societal benefit. If we do not do it, the effects——

Mr. GORE. I am willing to pay a lot of money——

Dr. CHAKRABARTY. It depends upon who you define in the society. If you ask me, who does not live in Love Canal, I would say, "Gee, I don't want it." However, if you ask a resident of Times Beach, "Yes," he might say, "I think that's a wonderful idea because I will be able to go back home."

Mr. GORE. We have a program called the Superfund that will pay lots of money to people that are going to clean up——

Dr. CHAKRABARTY. But that is the point I am trying to make—that it is the chicken and the egg story. Do we first try to give you a guarantee that the bugs I am going to use are not going to affect the ecology in any way, which I cannot, or do you let me use the bugs with all the previous judgment that you can make in terms of how does it affect the ecology? If the consensus is that such microorganisms should not really affect the ecology in a drastic way, that we should be allowed to go ahead and use the micro-organisms.

Mr. GORE. That is precisely the question that we are exploring here on this panel. It is not an easy one to answer. However, before the hearings are concluded and our report is published, we hope to have the outlines of a sensible answer.

Mr. Brown?

Mr. BROWN. Following up the line of discussion you have been conducting, Mr. Chairman, it seems to me that we do have a special circumstance with the sort of developments that Dr. Chakrabarty is talking about, where the micro-organism is aimed at reducing an existing hazard. That applies even to the oil-eating bug, as well as to those that destroy the other pollutants.

We have a situation where the hazard to the environment and to human beings, if nothing is done, may be far worse than anything we can conceive of if something goes wrong with the solution, the engineered bacteria.

I am suggesting that maybe we ought to define a special area of consideration where the purpose of the activity is to alleviate an even greater damage to either human health or the environment. There should be special circumstances that might apply there.

Does that idea seem reasonable, Dr. Chekrabarty?

Dr. CHAKRABARTY. I think it is perfectly reasonable, Mr. Brown.

As you said, in California, people have used moths, sterile moths, in order to get rid of some problems with other moths.

The question is, when you have to do it, there might be a little bit of chance, as you correctly point out, that there might be some nonsterile ones and they might cause additional problems. Nevertheless, there is a problem, and you have to take what measures you feel are appropriate.

I completely agree with you that there might be special circumstances, particularly when it comes to environmental pollution, mainly because of the fact that it affects only a very tiny segment of the society, and your reaction depends upon whether you belong to the affected society or whether you belong to the outside society. I think, in all fairness, also the fact is that it is really, although it appears to some people that it might be a limited pollution problem, my hunch is that it is going to be a very big pollution problem. At least we must find out whether the microbial technology can really solve the problem. If it can, I think we can avoid a lot of future problems.

Mr. BROWN. I like the suggestion that Dr. Hardy made that we should proceed on a step-by-step basis here. I think that is the reasonable way to proceed, but there are certain cautions that you have to observe. The step-by-step process should be one in which you evaluate the results of each step in an adequate way. If the testimony of the previous panel can be referred to, there may be situations in which we will take a step but we will not provide an adequate mechanism for evaluating all of what could be learned from that step.

For example, if we did not have an adequate ecological review, for whatever reason, but just looked at the human health aspects, we might miss something that would be pertinent when we finally decided it was safe to release such an organism on a large-scale basis.

All I am suggesting is that we should follow the best science that we can as we go through the step-by-step process. I do not suppose any of you would disagree with that.

I am reminded that, in the past, there has been a certain tendency on the part of scientists as they went step by step to assume that they were infallible, and they sometimes learned that they were not, with tragic consequences.

For example, and I do not want to belittle the chemical industry, but there have been times when they brought new products on the market in the early days, convinced that they had a beneficial effect but without an adequate evaluation, because we did not even know that the chemical might have a mutagenic or some other effect that we had never actually tested for. We could do the same thing in this field if we are not careful.

Certainly that has prompted you to make a comment, hasn't it, Dr. Hardy?

Dr. HARDY. I agree, certainly, with what you have said.

In the plant case, I think it is reasonable to proceed step by step. You will try to create, as you go down that road, situations that are like the field situation is going to be. You may want, if it is being produced like the kudzu case, to see what its competitiveness is with the rest of the environment. That is going to be more difficult as you go down the microbial area to define what are the most relevant experiments regarding competitiveness with the rest of the environment.

One thing that we have not considered here is, the experimentation here is a lot less gross, more defined than experimentation is that has been done up to this stage. We have been taking plants, two plants with very different genetic materials, putting them together, and doing plant breeding for years, and doing that successfully.

In most of these cases, it is very defined pieces of genes. We know exactly what we are adding here. I think that gives us an advantage over the examples that were used of gypsy moth, and so on, where that is a whole broad, new genetic component. We can intelligently go in and say we have added just "*x*."

I am not familiar with specifically what Dr. Chakrabarty has added, but I think it is probably a very defined situation. Then that will suggest, I think, more logical experiments that one can do to avoid a major problem that could occur down the road.

Mr. BROWN. Mr. Hardy, I wanted to comment—this is not by way of questioning, but I find your discussion of developments in agricultural science to be extremely interesting and stimulating. As you perhaps know, I am planning rather extensive hearings on oversight of agricultural research in the agricultural community and wondered perhaps if you had been invited to appear before those hearings.

Dr. HARDY. I have not been at this time.

Mr. BROWN. Maybe that is just an oversight. [Laughter.]

You made reference to the effect of CO_2 on productivity of certain plants, and we have been wrestling with what we call the CO_2 problem in this committee for a long time.

I gather from your statement that there is a beneficial effect from an overabundance of CO_2 in the atmosphere and that you are trying to do something genetically to produce that same effect as the overabundance of CO_2 produces?

Dr. HARDY. Yes. In the atmosphere, there is something in excess of 300 parts per million of carbon dioxide. That has been going up about 1 part per million per year, presumably due to the burning of fossil fuels.

If you increase carbon dioxide, say double it to 600 parts per million or to 900 parts per million, you will get major increases in the growth of most major crop plants, such as wheat, rice, soybeans, and so on. Therefore, there is a compensating effect that will occur.

One would like to get that same benefit occurring, however, at 300 parts per million, and the yield responses there could be rather fantastic. That is one of the big opportunities in agricultural biotechnology.

Mr. BROWN. Thank you very much.

Mr. GORE. Congressman MacKay?

Mr. MACKAY. Thank you, Mr. Chairman.

I am not burdened with an excess of facts in this area. I come with a great deal of ignorance.

It strikes me that what we have is some very responsible people who are representing extremely responsible institutions, and as long as it stays this way, we have a problem which is probably resolved OK with guidelines as to the private sector that are voluntary.

Let me pose a hypothetical that this industry, like computers and a lot of others, takes off and that it turns out you really do not need a Du Pont to support you, and it turns out that people are able to intuitively figure where the next step is, and it turns out that then small companies, who do not care about insurance because they can take bankruptcy if something goes wrong, get into a race and they are really trying to find out what is going to happen next.

Is that hypothetical strictly wild. What if, for instance, Dr. Lindow, it turns out I am a citrus grower and I like what you are doing? What if it turns out that that crazy thing that makes ice form also has some other function, a bizarre function, or that by replacing that gene you get a new function? What if it turns out some of your graduate students say, "My gosh, I can be the next genetic," and they go a little wild? They do not care about insurance. There is $200 or $300 million to be made just by taking the idea public, and it turns out, since they are in the private sector, they do not have to comply with anything.

Now can you tell me that what we have now is a reasonable, from the standpoint of the public, regulatory mechanism? To me, what we have is something based on the assumption that this thing is always going to be done by academics; that there is not a profit motive in the world; and that the insurance industry somehow, since it makes its living looking backward and you cannot see any of this looking backward, it is going to refuse to insure any of it—we all understand that—that they are somehow going to protect the public. I think the whole assumption is bizarre. I do not think it makes any sense at all.

I would like your comments.

Dr. LINDOW. Maybe I can just comment. We certainly found the requirement to go before the RAC committee both traumatic but instructive in the same sense. Certainly, we would not like to see legislation that would be too restrictive on the research aspect of the scientific aspects.

Mr. MACKAY. Nor would I.

Dr. LINDOW. At the same time, I think that we did find it a very instructive experience. The peer review system that is inherent throughout much of science and that of evaluation of peer's research seems to have worked fairly well over the years, and we feel it would be similarly constructive to see that it would be in place in this sort of situation.

Mr. MACKAY. It is difficult to mandate that everybody has to go through peer review.

Dr. LINDOW. If such legislation could be constructed to make sure that it was not inhibitory and that peers could be selected that could be both progressive and responsive, I think that that would be an ideal situation.

Mr. BROWN. All of you gentlemen have been through this process. Could you just indicate very briefly to what degree you have voluntarily had your research peer reviewed from the standpoint of possible hazards to the environment or human beings, or whatever unexpected or unknown results might come about?

Did you go through such a process in your work? Do you normally do that? Do you feel that you have done it adequately or are you so confident that you know everything there is to know that you have proceeded without a systematic review of this thing?

Dr. LINDOW. Everybody tries to be as systematic as possible. Really, many complaints of scientists is that they tend to give grey answers rather than black or white. Really, the situation that we are dealing with here is trying to estimate and minimize the risks involved with these experiments.

In that end, we have attempted to try to measure the right types of parameters that we can foresee and our fallibility, too, to be able to estimate such risks.

In the process of appearing before the RAC committee for permission to release our micro-organisms, we have had to pull together these assessments and put it before peer review. We feel that it is as good as we could expect in this technology.

Mr. MACKAY. The gentlemen in the first panel talked about law and the necessity for a standard of care. It would seem to me that legislation would at least eliminate a lot of the question as to what is the proper standard of care to which you should go. From the standpoint of a Du Pont or anyone else, it would begin to set the stage so that the insurance industry could begin to make rational judgments. I did not mean to belittle the insurance industry. Clearly, there is going to have to be a way to evaluate that risk. Setting a legislative standard of care would seem to me to be one of the first things you would do in this framework.

Dr. Hardy, how does Du Pont deal with those whole issue. You are distinctive to me on the panel in that you are representing a private sector operation that presumably is in business for a profit and has clearly done quite well at it.

Dr. Hardy. My concern in legislation is that it will be overly restrictive and not adequately fluid to deal with the real hazards. It will be constructed in time and set in concrete. That will impede, I think, the advancement of the field, the ability of U.S. industry to compete with the rest of the world, and the rest of the world is becoming aggressive in biotechnology, and I am not convinced that legislation will accomplish more for society than has an approach such as the guidelines.

The history on the guidelines is very, very good at this stage. You could have raised the same questions about a little Genentech and a little Cetus if we were sitting here 5 years ago. They have abided by the guidelines, as I understand it, voluntary compliance, and I am not aware of anything that occurred in any of the small companies in the health area that has been a problem either to the workers at this stage or to society at this stage. The problem we are dealing with in agriculture is a little different one—we are not as concerned with the worker or the personnel. We are now concerned with what is the impact going to be on the environment.

At the time that the guidelines were put together, I can recall sitting with other people like Peter Day, who is now head of the Plant Breeding Institute in the United Kingdom—he was in the United States at that time—constructing subsets to the guidelines that would relate to the plant area as far as doing the experiments without release.

It may be appropriate at this stage that we now sit down and define how should these be modified for release into the environment.

Mr. MacKay. Do you see this field undergoing an exponential growth as people begin to make the intuitive steps from the basic work that is being done now? Do you see the potential threat to the public or the environment growing exponentially?

Dr. Hardy. Certainly, the work one would expect to grow exponentially. The possibilities are large.

As we gain more information, the risk to the public, I think, is going to go down. Again, I am basing that on the experience of the work that has been done in the health care-related field. I think there is less risk certainly to workers now—we are aware there is less risk—than 5 years ago. I would expect the same sort of thing to occur as we get more experience in this area.

Mr. MacKay. Thank you, Mr. Chairman.

Mr. Gore. Congressman Volkmer?

Mr. Volkmer. I would just like to ask, for familiarization, in the event that, Dr. Hardy, you are able to come up with micro-organisms or bacteria, or whatever, to get rid of the corn root worm that would be able to impregnate itself in the soil and disease the root worm and it dies. Is there anything presently in the Government that would control your use of that?

Dr. Hardy. Bacillus thuringensis is probably the relevant example here. Bacillus thuringensis is a bacteria that produces a pesticide. That material is marketed not by my company, but by a few other companies. My understanding there is that FIFRA had to be gone through in bringing that to the market.

Mr. Volkmer. Was that marketed, basically, then, as a chemical?

Dr. Lindow. It was marketed, basically, as a pesticide.

Mr. **Volkmer**. As a pesticide. Then FIFRA would have jurisdiction over that?

Dr. **Hardy**. Exactly.

Mr. **Volkmer**. We have a lot of dioxin in Missouri. We want to degrade it. Dr. Chakrabarty, let's say that you come up with a solution, a micro-organism or something to assist degradation of dioxin in the soil, which I would love for you to do, would you have to go through any process in order to utilize it?

Dr. **Chakrabarty**. It is not clear, Mr. Volkmer, and that is why I want defined guidelines, because we do talk to people, particularly chemical industry people who have been accused by the EPA of having toxic dumpsites or something like that. It is somewhat frustrating that you do not really know, even if you have a micro-organism that can do it, as to how to use it.

The question has been raised, and let me amplify this a little bit, if I may. Any time we talk about a new micro-organism, we think that something must be wrong with it; it must be hazardous or something.

As an individual scientist, every time I want to see the degradation of a new compound, I go to nature, pick up a micro-organism that can degrade it, grow it in large amounts, do genetic experiments, throw it all the time into the environment through the sink.

As far as I know, thousands of scientists do it and, as far as I know, there has been no single incident that any havoc has been created.

You must not think that all those micro-organisms in nature are all dangerous, and if you pick one of them, purify them and grow them, it is going to cause problems.

If you remember that, if you will keep that in the back of your head, then you will say, "Well, this guy is picking up one of those micro-organisms," that micro-organism, however, cannot degrade dioxin. Therefore, the only thing he is really doing is manipulating that micro-organism so that now it can degrade dioxin. What are the probabilities that that micro-organism is going to cause problems for the human being? When I ask myself that, I find that the probability is essentially zero, although not totally zero because I cannot ever say it would not cause any problem.

That is why I am saying that, given the fact that micro-organisms might be of tremendous benefit to the society, there is really very low risk in terms of using them in an affected area.

Shouldn't we have guidelines—and, remember, when I say "guidelines," I do not mean that I will just make the decision to go and use it. I am talking about a body just like RAC—maybe we may even go to RAC—with ecologists, microbiologists, geneticists, lawyers, whoever you want to have as members. I would simply have access to these people, explain to them what the micro-organism can do; what the magnitude of the problem is in Love Canal or Times Beach, or whatever; that as far as I can determine by doing a lot of toxicological tests that there is nothing wrong with the micro-organism; that may I now go and use it and see if I can solve the problem. So long as I can accomplish this, that is all I really care for and that is all I need your help for.

Whether you come up with legislation telling me to do it or guidelines, or whatever, is totally up to you.

Mr. VOLKMER. The last question, Dr. Lindow, in your field in plants, through reproduction of genes you are able to come up with a 2-foot long banana. Do you have to go through USDA or any process—would you have to—in order to start selling your new banana plant, that you don't have to go to Central America but you can grow them in Florida?

Dr. LINDOW. We do not specifically work with bananas, but I would suspect that most amendments that we would come up with in terms of micro-organisms would be considered a pesticide that would have some sort of an effect on some target. Many of these such organisms would fall under the existing——

Mr. VOLKMER. Pesticides would go under FIFRA.

Dr. LINDOW. It would go through FIFRA; right.

Mr. VOLKMER. Thank you, Mr. Chairman.

Mr. GORE. Thanks to our witnesses on this panel. We appreciate your testimony here. You have helped us to understand the subject a great deal. We appreciate it very much. Thank you.

Our third panel is made up of Dr. Bernard Talbot, Deputy Director of the National Institute of Allergy and Infectious Diseases at NIH; Mr. Don Clay, Acting Assistant Administrator for Pesticides and Toxic Substances at the Environmental Protection Agency; and Dr. Edgar Kendrick, Acting Deputy Assistant Secretary for Science and Education at the U.S. Department of Agriculture.

Gentlemen, if you will come forward to the witness table, I am going to ask my cochairman, Mr. Walgren, to take over at thi point.

Mr. WALGREN. Let me say at the outset that your statements will be made part of the record. I would like to ask you, on behalf of the committee, to summarize or outline your statements in some reasonable timeframe in view of the hour.

Let's proceed with Dr. Talbot.

STATEMENT OF DR. BERNARD TALBOT, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD.

Dr. TALBOT. The NIH guidelines for research involving recombinant DNA molecules are safety standards which were developed in response to a request by scientists that the National Institutes of Health devise such guidelines.

Overseeing the NIH guidelines is the NIH Recombinant DNA Advisory Committee, called RAC for short. The RAC consists of 25 voting members, scientists of many different disciplines, although as pointed out earlier today not presently including an ecologist, plus laymen appointed by the Secretary of Health and Human Services, plus nonvoting representatives of Federal agencies who participate actively in the RAC meetings. The voting members include a lawyer, a former State legislator, an occupational safety expert, practicing physicians, the executive director of a State department of health, and numerous scientists.

Federal agencies with representatives on the RAC include: The National Science Foundation, the Department of Agriculture, EPA, the Food and Drug Administration, the Department of State, the Veterans' Administration, the Department of Energy, CDC, and the National Institute for Occupational Safety and Health.

Any proposed revisions of the NIH Guidelines must first be published for public comment, and then discussed and voted on by the RAC in open session, before they may be adopted by NIH.

The NIH Guidelines were first issued in July 1976. Those original guidelines included classes of experiments that were "not to be performed," including "deliberate release into the environment of any organism containing a recombinant DNA molecule."

The first revision of the NIH Guidelines, in December 1978, reorganized the classes of experiments previously listed as "not to be performed" into a section called "Prohibitions," again including "deliberate release into the environment of any organism containing recombinant DNA." However, they noted that, "Experiments in these categories may be excepted from the prohibitions * * * provided that these experiments are expressly approved by the Director, NIH, with advice of RAC after appropriate notice and opportunity for public comment."

The revision of the Guidelines issued in April 1982 changed that section from one called "Prohibitions" to one called "Experiments that Require RAC Review and NIH and Institutional Biosafety Committee Approval Before Initiation." Still in this category was "deliberate release into the environment of any organism containing recombinant DNA."

The most recent revision of the Guidelines, issued June 1, specifies new procedures to facilitate the approval of field testing under certain specified conditions of certain plants modified by recombinant DNA techniques. These now require review by the RAC Plant Working Group, but no longer by the full RAC, prior to approval by NIH.

In addition to review by the full RAC, or the Plant Working Group, prior to approval by the NIH, any deliberate release to the environment also requires prior approval by the local institutional biosafety committee [IBC].

To date, three cases of deliberate release to the environment have been approved by NIH. In each case:

Notice was first placed in the Federal Register at least 30 days prior to the RAC meeting, giving notice and inviting public comment.

The proposal was then discussed at an open session of the RAC, with active participation in the discussion by the Department of Agriculture representative and representatives from other Federal agencies. During the discussion the RAC carefully considered the possible hazards of the experiment. This involved some RAC members proposing "scenarios" of how they felt possible hazards might result from the experiment, and other RAC members replying as to why the scenarios were extremely unlikely to occur. Following the discussion, the RAC voted in each of the three cases to recommend approval of the proposal.

In each of these three cases advice was sought subsequently from the Department of Agriculture Recombinant DNA Advisory Committee, which in each of the three cases recommended approval of the proposal.

Finally, NIH published a notice in the Federal Register explaining the request and the reasons why it had granted approval.

During the 95th Congress there were 16 different bills dealing with recombinant DNA introduced. Hearings were held before two different subcommittees in the House and two in the Senate. The most extensive set of hearings were held here by the House Subcommittee on Science, Research and Technology, chaired at that time by Congressman Ray Thornton. After leaving Congress, Mr. Thornton was subsequently a member and then the chairman of the NIH Recombinant DNA Advisory Committee.

Bills which would have made the NIH Guidelines mandatory for the entire country passed committees in both the House and the Senate but never reached the floor of either the House or the Senate for a vote. There is today, therefore, no national law making the NIH Guidelines mandatory for private industry.

In the absence of national legislation, New York State and a number of localities have passed local legislation making the NIH Guidelines mandatory. For the rest of the country, other than these localities, for work not supported by Federal funds, compliance with the NIH Guidelines is not mandatory. There is, however, a section of the NIH Guidelines entitled, "Voluntary Compliance," which encourages commercial organizations to comply voluntarily with the Guidelines. Currently 52 private companies have registered their IBC's with NIH and received verification from NIH that their IBC membership meets the requirements of the Guidelines.

Previous versions of the Guidelines required that all recombinant DNA experiments over 10 liters in volume be reviewed by the RAC and approved by NIH. During the time that this provision was in effect, private companies voluntarily submitted proposals to NIH to exceed 10 liters in volume.

These were reviewed by the RAC in closed session to protect proprietary information voluntarily submitted. Any future request submitted by a commercial firm requesting RAC review of plans to deliberately release organisms containing recombinant DNA into the environment would be brought to RAC for review. If this involves proprietary information, and review by the RAC in closed session is requested by the company, such a closed session review would be held.

This concludes my prepared testimony. I will be pleased to answer any questions.

[The prepared statement of Dr. Talbot follows:]

Testimony by Dr. Bernard Talbot, to be given June 22, 1983, at joint hearing of the Subcommittees on Science, Research and Technology and on Investigations and Oversight of the Committee on Science and Technology, U.S. House of Representatives, on "Environmental Implications of Genetic Engineering."

I am Dr. Bernard Talbot, Deputy Director of the National Institute of Allergy and Infectious Diseases, at the National Institutes of Health. I have been associated, since 1975, with the original preparation, and with all subsequent revisions, of the NIH Guidelines for Research Involving Recombinant DNA Molecules. These safety standards were developed in response to a request by scientists[1] that the National Institutes of Health devise "guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules."

Overseeing the NIH Guidelines is the NIH Recombinant DNA Advisory Committee (called RAC for short). The RAC consists of 25 voting members (scientists of many different disciplines plus laymen) appointed by the Secretary of Health and Human Services, plus non-voting representatives of Federal agencies[2] who participate actively in the RAC meetings. The voting members include a lawyer, a former State legislator, an occupational safety expert, practicing physicians, and the executive director of a State department of health. Federal agencies with representatives on the RAC are the: National Science Foundation; Department of Agriculture; Environmental Protection Agency; Food and Drug Administration; Department of State; Veterans Administration; Department of Energy; Centers for Disease Control; National Institute for Occupational Safety and Health; Department of Commerce; Department of Interior; Department of Transportation; and National Aeronautics and Space Administration.

Any proposed revisions of the NIH Guidelines must first be published for public comment, and then discussed and voted on by the RAC in open session, before they may be adopted by NIH.

The NIH Guidelines were first issued in July 1976.[3] Those 1976 Guidelines included classes of experiments that were "not to be performed." This included "deliberate release into the environment of any organism containing a recombinant DNA molecule."

The first revision of the NIH Guidelines, issued in December 1978[4] reorganized the classes of experiments previously listed as "not to be performed" into a section entitled "Prohibitions" including "deliberate release into the environment of any organism containing recombinant DNA." However, the Guidelines noted that "Experiments in these categories may be excepted from the prohibitions . . . provided that these experiments are expressly approved by the Director, NIH, with advice of the Recombinant DNA Advisory Committee after appropriate notice and opportunity for public comment."

The revision of the Guidelines issued in April 1982[5] changed the section entitled "Prohibitions" to one entitled "Experiments that Require RAC Review and NIH and Institutional Biosafety Committee Approval Before Initiation." Included again under this category was "deliberate release into the environment of any organism containing recombinant DNA."

The most recent revision of the Guidelines, issued three weeks ago[6] specifies new procedures to facilitate the approval of field testing under certain specified conditions of certain plants modified by recombinant DNA techniques; these now require review by the RAC Plant Working Group, but no longer by the full RAC, prior to approval by NIH.

In addition to review by the full RAC, or the RAC Plant Working Group, prior to approval by the NIH, any deliberate release to the environment also requires prior approval by the local institutional biosafety committee.

To date three cases of deliberate release to the environment have been approved by NIH. In each such case:

(1) Notice was placed in the Federal Register at least 30 days prior to the RAC meeting at which the proposal was discussed, giving notice and inviting public comment on the proposal.

(2) The proposal was discussed at an open session of a RAC meeting, with active participation in the discussion by the Department of Agriculture representative. During the discussion the RAC carefully considered the possible hazards of the experiment. This involved some RAC members proposing "scenarios" of possible hazard, and other RAC members replying as to why the "scenarios" were extremely unlikely to occur. Following the discussion, the RAC voted in each of the three cases to recommend approval of the proposal.

(3) Advice was sought from the Department of Agriculture Recombinant DNA Advisory Committee which in each of the three cases recommended approval of the proposal.

(4) NIH approved each of the proposals with a notice in the *Federal Register* explaning the request, and the reasons for granting approval.

The three cases are: approval to Dr. Ronald Davis of Stanford University[7] to field test corn plants transformed by corn DNA; approval to Dr. John Sanford of Cornell University[8] to field test tomato and tobacco plants transformed with bacterial and yeast DNA; and approval to Drs. Nickolas Panopoulos and Steven Lindow of the University of California, Berkeley[9] to release *Pseudomonas syringae* and *Erwinia herbicola* carrying deletions in the genes involved in ice nucleation, for purposes of biological control of frost damage in plants.

During the 95th Congress (1977-1978) sixteen different bills dealing with recombinant DNA were introduced. Hearings were held before two different subcommittees in the House and two in the Senate. The most extensive set of hearings[10] were held by this House Subcommittee on Science, Research and Technology, chaired at that time by Congressman Ray Thornton. (After leaving Congress, Mr. Thornton subsequently was a member (1979-1982) and Chairman (1980-1982) of the NIH Recombinant DNA Advisory Committee). Bills which would have made the NIH Guidelines mandatory for the entire country passed Committees in both the House and Senate but never reached the floor of the House or Senate for a vote. There is therefore today no national law making the NIH Guidelines mandatory for private industry. In the absence of national legislation, New York State and a number of localities[11] have passed local legislation making the NIH Guidelines mandatory. For the rest of the country other than these localities, for work not supported by Federal funds, compliance with the NIH Guidelines is not mandatory. There is, however, a section of the NIH Guidelines entitled "Voluntary Compliance" which encourages commercial organizations to comply voluntarily with the Guidelines. Currently 52 private companies have registered their Institutional Biosafety Committee (IBC) with NIH and received verification from NIH that their IBC membership meets the requirements of the Guidelines. Previous versions of the Guidelines required that all recombinant DNA experiments over 10 liters in volume be reviewed by the RAC and approved by the NIH. During the time that this provision was in effect, private companies voluntarily submitted proposals to NIH to exceed 10 liters. These were reviewed by the RAC in closed session to protect propietary information voluntarily submitted. Any future request submitted by a commercial firm requesting RAC review of plans to deliberately release organisms containing recombinant DNA into the environment would be brought to RAC for review; if this involves proprietary information, and review by RAC in closed session is requested by the company, such a closed session review will be held.

This concludes my prepared testimony. I will be pleased to answer any questions.

FOOTNOTES

1 "Potential Biohazards of Recombinant DNA Molecules" appeared simultaneously in Science 185, 303, 1974; Nature 250, 175, 1974, and the Proceedings of the National Academy of Sciences. 71, 2593, 1974, by Drs. Paul Berg, David Baltimore, Herbert Boyer, Stanley Cohen, Ronald Davis, David Hogness, Daniel Nathans, Richard Roblin, James Watson, Sherman Weissman and Norton Zinder.

2 The representatives of Federal agencies to the NIH Recombinant DNA Advisory Committee are: Dr. Herman Lewis, Senior Scientist for Recombinant DNA, National Science Foundation; Dr. Sue Tolin, Cooperative State Research Service, Department of Agriculture; Dr. Morris Levin, Director, Office of Explorative Research, Environmental Protection Agency; Dr. Henry Miller, National Center for Drugs and Biologics, Food and Drug Administration; Dr. William Walsh, Biomedical Research Liaison and Health Affairs Officer, Department of State; Dr. Richard Green, Director, Medical Research Service, Veterans Administration; Dr. George Duda, Office of Health and Environmental Research, Department of Energy; Dr. Walter Dowdle, Director, Center for Infectious Diseases, Centers for Disease Control; Dr. Richard Lemen, Director, Division of Standards Development and Technology Transfer, National Institute for Occupational Safety and Health; Mr. John Cox, Bureau of Industrial Economics, Department of Commerce; Dr. Mariano Pimentel, Medical Director, Department of the Interior; Dr. George Cushmac, Research and Special Programs Administration, Department of Transportation; Dr. Donald DeVincenzi, Chief, Research and Technology Development, National Aeronautics and Space Administration.

3 NIH Guidelines for Research Involving Recombinant DNA Molecules. Federal Register, July 7, 1976, Part II, pages 27902-27943.

4 NIH Guidelines for Research Involving Recombinant DNA Molecules. Federal Register, December 22, 1978, Parts VI and VII, pages 60080-60131.

5 NIH Guidelines for Research Involving Recombinant DNA Molecules. Federal Register, April 21, 1982, Parts II and III, pages 17166-17198.

6 NIH Guidelines for Research Involving Recombinant DNA Molecules. Federal Register, June 1, 1983, Parts II and III, pages 24548-24581.

7 Approval appeared in the Federal Register, August 7, 1981, page 40331.

8 Approval appeared in the Federal Register, April 15, 1983, page 16459.

9 Approval appeared in the Federal Register, June 1, 1983, page 24549.

10 Hearings before the Subcommittee on Science, Research and Technology, Committee on Science and Technology, U.S. House of Representatives, on "Science Policy Implications of DNA Recombinant Molecule Research." Hearings held on March 29, 30, 31; April 27, 28; May 3, 4, 5, 25, 26; and September 7 and 8, 1977.

11 Localities requiring compliance with the NIH Guidelines are: Amherst, Massachusetts; Berkeley, California; Boston, Massachusetts; Cambridge, Massachusetts; Emeryville, California; Newton, Massachusetts; Princeton, New Jersey; Somerville, Massachusetts; and Waltham, Massachusetts.

CURRICULUM VITAE

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1958 - B.A. - Columbia College
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1967-1969	Postdoctoral Fellow, Department of Biology, Massachusetts Institute of Technology
1969-1970	Postdoctoral Fellow, University of Rome, Italy
1970-1971	Grants Associate, Division of Research Grants, National Institutes of Health (NIH)
1971-1972	Medical Officer, Viral Carcinogenesis Branch, National Cancer Institute (NCI), NIH
1972-1974	Medical Officer and Vice-Chairman, Tumor Virus Detection Segment, NCI, NIH
1974-1975	Acting Associate Chief, Viral Leukemia and Lymphoma Branch, NCI, NIH
1975-1978	Special Assistant for Intramural Affairs, NIH
1978-1981	Special Assistant to the Director, NIH
1981-date	Deputy Director, National Institute of Allergy and Infectious Diseases (NIAID), NIH

Mr. **Walgren**. Thank you, Dr. Talbot.
Mr. Clay?

STATEMENT OF DON R. CLAY, ACTING ASSISTANT ADMINISTRATOR, OFFICE OF PESTICIDE AND TOXIC SUBSTANCES, ENVIRONMENTAL PROTECTION AGENCY, WASHINGTON, D.C.

Mr. **Clay**. Good afternoon.

First, let me thank you for the opportunity to be here today. Earlier speakers have discussed some of the uncertainties and the possible health and environmental risks associated with commercialization of recombinant DNA technology. In my testimony I will focus on the role of the U.S. Environmental Protection Agency in reviewing and, if necessary, controlling these risks. I will begin by discussing the applicability of the Federal Insecticide, Fungicide, and Rodenticide Act, known as FIFRA, and the Toxic Substances Control Act, or TSCA, to genetically engineered substances. I will then review the major issues related to the possible oversight of biotechnology under these laws, describe the actions EPA has taken to date, and discuss the future roles we may be playing in this emerging field. At the conclusion, I will be pleased to answer any questions. I will summarize my rather lengthly statement.

FIFRA and TSCA are the two EPA authorities most applicable to the review of genetically engineered substances before their commercialization. Both of these laws are administered by the EPA Office of Pesticide and Toxic Substances, OPTS. FIFRA, as its name indicates, applies to pesticides; TSCA applies to most other commercial chemical substances with the important exception of drugs and food additives. I will discuss each of these in turn.

FIFRA, which is administered within OPTS by the Office of Pesticide Programs, OPP, requires premarket testing of all pesticides and regulates their use. It, therefore, provides clear authority to regulate genetically engineered pesticidal products.

Over the past 10 years, OPP has evaluated and registered about a dozen of the more traditional, nonengineered microbial agents for use in agriculture, forestry, and mosquito control. As a result, we have gained considerable experience in evaluating risks associated with the use of naturally occuring microbial entities, such as bacteria, viruses, for pesticidal purposes. However, we have no experience yet with genetically engineered products.

The industry is currently developing pesticides using recombinant DNA technology, and we expect submission of the first application for registration, or for an experimental use permit, within the next 18 to 24 months. Registrants will be required to comply with OPP's data requirements which are specified in pesticides registration proposed data requirements: Part 158, which includes standards developed for microbial pesticides. These standards, which require product analysis, human safety, and ecological effects data, are adequate for the assessment of nonengineered pesticides. However, more extensive data or information may be necessary to evaluate genetically engineered pesticides. The regulation establishing these data requirements explicitly provides the necessary flexibility to require additional data if OPP determines a need for it.

As we gain knowledge and experience from registering genetically engineered pesticides, it is likely that these data requirements will be modified or expanded. In any case, OPP will be working closely with registrants encouraging them to meet with us before they submit their applications. so that we can determine whether any additional data will be necessary to evaluate their products.

Turning now to TSCA, the Toxic Substances Control Act, which was enacted in 1976, is designed to regulate chemical substances in any applications not specifically covered by other regulatory authorities. As a result, products of genetically engineered use for such purposes as pollution control or extraction and production of enzyme for industrial uses would likely fall under the jurisdiction of TSCA.

The most significant section of TSCA which can be applied to genetically engineered substances is section 5. Section 5 is a powerful tool because it requires agency review of new substances prior to manufacture before there is a problem, before the substance enters commerce and our environment. It gives EPA significant authority to control risks and to insure that adequate data to assess risks are developed on these substances before commercialization.

Over the past several months EPA has been reviewing the applicability of these requirements to the products or recombinant DNA technology, including the micro-organisms themselves. Our preliminary conclusion from this review is that genetically engineered substances are subject to TSCA. Although the law is silent on this matter, the legal reasons supporting TSCA applicability appear compelling.

Perhaps the most important argument in favor of TSCA oversight of biotechnology is that it is consistent with the traditional TSCA role of reviewing new chemical substances before they are put to widespread use. The genetic material of life, DNA, fits the legal definition of a chemical substance under TSCA. Using genetic-engineered techniques to change DNA results in recombinant DNA, a new chemical substance. Therefore, recombinant DNA appears to be a new chemical substance under section 5 of TSCA.

This premanufacturing review requirement is one of the most powerful of TSCA's tools, and it could fill important needs in reviewing genetically engineered organisms before they are released into the general environment.

In addition to the statutory argument, there is a policy argument for invoking TSCA authority. Congress intended TSCA to fill the gaps where other health and environmental statutes leave off. Other statutes besides TSCA, such as the Clean Water Act and the Clean Air Act, may apply to specific questions related to biotechnology, and OTS has begun to work with the EPA office which administers these acts to insure a coordinated approach. However, to the extent other offices do not or cannot regulate biotechnology, the responsibility comes under TSCA authority.

Another policy consideration supporting the TSCA role in this area is that its comprehensive data development provisions give EPA broad authority to monitor the production, use, and exposure of chemical substances. These provisions may be very useful in gathering data or requiring the health and environmental testing of recombinant DNA.

Although TSCA and FIFRA appear to provide authority to oversee recombinant DNA technology, there are numerous complex issues which EPA must address in implementing those authorities. For example, there is considerable uncertainty concerning which, if any, areas of recombinant DNA technology will require regulatory controls and what these controls should be. Clearly, more analysis is needed here.

A related technical problem is that there is almost no accepted methodologies for evaluating the safety of genetically engineered products. At a minimum, we must develop methodologies to evaluate environmental fate, human and environmental exposure, and potential environmental and health hazards of genetically engineered organisms.

To address this question, OTS has obtained funding commitments from our Office of Research and Development which will support the development of test methodologies to evaluate the safety of bioengineered products. The data requirements and testing methods will be useful to the Office of Pesticide Programs, the Office of Toxic Substances, and other EPA programs that may eventually become involved in assessing the safety of bioengineered products. They will also be very important to industry, because it will ultimately be industry's responsibility to develop safe products.

As an aside, EPA's Office of Research and Development is conducting a research into potential environmental applications of biotechnology. Because the committee requested the information on recombinant DNA regulatory issues, I will not discuss these research endeavors today, but the information is available, if you require it.

In addition, we have placed a high priority on coordinating our activities with those of other regulatory offices. OPTS has initiated an agencywide working group to explore program issues raised by biotechnology. The offices involved in this effort include Pesticides and Toxic Substances, Drinking Water, Water Regulations and Standards, Solid Waste, Research and Development, and the Office of the General Counsel.

OPP and OTS are also coordinating their activities with other agencies. For example, we have contacted the Food and Drug Administration, the Department of Agriculture, the National Institutes of Health, and the Occupational Safety and Health Administration, among other agencies, to determine the status of their current activities and take advantage of their expertise.

Besides working with other Government groups, we are seeking public and industry participation in discussions relating to biotechnology. We have spoken with the Industrial Biotechnology Association, and we plan to work with its members more extensively in the future. EPA has also entered into a cooperative agreement with the American Association for the Advancement of Science to sponsor a symposium series on the scientific, economic, and legal aspects of biotechnology, and we are using the Administrator's Toxic Substances Advisory Committee to insure public participation and to provide access to expert opinions.

Finally, I want to emphasize at this point we recognize the adequate oversight of recombinant DNA under TSCA and FIFRA may require considerable commitment of resources, particularly because of the technical uncertainties in this area. We are prepared to make the necessary commitments to educate existing staff, recruit new expertise as is needed, and develop an effective biotechnology program.

Although our resource needs depend on decisions which are still evolving, we are prepared to take a responsible role in evaluating to the extent necessary, controlling the products of biotechnology.

Thank you for your attention. I would be pleased to answer any questions when you are ready.

[The prepared statement of Mr. Clay follows:]

STATEMENT OF DON R. CLAY
ACTING ASSISTANT ADMINISTRATOR,
OFFICE OF PECTICIDE AND TOXIC SUBSTANCES
BEFORE THE
SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY
AND
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT
COMMITTEE ON SCIENCE AND TECHNOLOGY
HOUSE OF REPRESENTATIVES

JUNE 22, 1983

Good morning. First let me thank you for the opportunity to be here today.

I would like to begin today by attempting to clarify our understanding of the term "biotechnology". Next, I will talk about the environmental and health issues which biotechnology has raised at EPA, especially in the Office of Pesticides and Toxic Substances (OPTS). I will discuss the applicability of the Federal Insecticide, Fungicide, and Rodenticide Act, and the Toxic Substances Control Act. Then I will review the other factors which are influencing our biotechnology policies in EPA, brief you on the actions we have taken to date, and discuss the future roles we may be playing in this emerging field. At the conclusion, I will be pleased to answer any questions you may have.

I. SCOPE OF REGULATORY CONCERN IN BIOTECHNOLOGY

In its broadest meaning, biotechnology is the application of biological science towards technological ends, towards the production of chemicals or life forms which have potential commercial uses. It includes a diverse spectrum of activities, ranging from simple and clearly safe techniques such as the use of yeast to make alcoholic beverages and bread, to the complex recent technologies of gene splicing to create modified life forms and biochemicals. However, such a broad definition is not very useful for regulatory purposes since the familiar biotechnologies do not raise public or governmental concerns. Therefore, OPTS is giving primary attention to the applications of genetic engineering which involve modified life forms and substances which do not occur in nature. This definition accounts for the primary risk which such substances pose, namely, that they are "exotic" and therefore less likely to find natural enemies in our bodies or our environment.

Our most serious concerns have to do with the prospect of modified life forms being sold, distributed and used in the open environment, where they would be particularly difficult to control. In some cases, these organisms will be put into the environment intentionally, as when we use microbes to digest oil spills or we use viruses to control agricultural pests. In other cases they may be dispersed by accident or inadvertent escape. In both cases, genetically engineered organisms will present us with a host of environmental and public health concerns.

Fortunately, these types of "open environment" applications are not yet widespread. OPTS' Office of Pesticide Programs (OPP) has received and approved applications for microbial pesticides which will be used in the open environment, but none to date have been genetically engineered. OPTS' Office of Toxic Substances (OTS) has reviewed premanufacture notices for new chemicals produced by biological organisms, but we do not expect to see organisms containing recombinant DNA in widespread industrial use for at least several more years.

Some examples of the uncertainties which our scientists have raised about these products will illustrate why it is desirable to have government review prior to commercialization. One unknown is whether genetically engineered organisms, released into the environment, can be infective or toxic to humans or other organisms. Although we think the probability of this is low in most cases, an organism which has received a portion of its DNA from a pathogenic or toxic organism could potentially develop, or express, those traits. Another unknown is the possibility that a genetically modified organism could disrupt existing ecosystems. We have analogous experiences with the so-called "exotic" plants and animals: life forms which have come from environments where they had natural controls, and are introduced into new environments where they do not have natural controls. Disruption of ecosystems is not the norm in such cases, but it does occur. Examples which have become significant pests in the

United States are the kudzu weed, the chestnut blight, and the gypsy moth. Unfortunately, we have no clue at this time whether similar events are probable with genetically engineered microbes, nor how to estimate or minimize the risk if it does exist.

Given that there may be significant health and safety consequences which need to be investigated before genetically engineered substances are widely released into the environment, the next question is whether the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), and the Toxic Substances Control Act (TSCA) provide legal tools with which to regulate in this area.

II. FIFRA

FIFRA, which is administered by the Office of Pesticide Programs (OPP), provides authority to regulate genetically engineered pesticidal products. FIFRA requires premarket testing of all pesticides, including microbials, and regulates their use.

Over the past 10 years, OPP has evaluated and registered about a dozen of the more traditional, non-engineered microbial agents for use in agriculture, forestry and mosquito control. As a result, we have gained considerable experience in evaluating risks associated with the application in the environment of naturally occurring microbial entities (e.g. bacteria, viruses, fungi, protozoa) for pesticidal purposes. However, we have no experience yet with genetically engineered products.

Although no genetically engineered microbial pesticides have been submitted to OPP for registration, industry is currently developing pesticides using recombinant DNA technology and we expect submission of the first application for registration (or for experimental use) within the next 18-24 months. OPP will be working closely with registrants, encouraging them to meet with our representatives prior to submission of their applications to discuss their product and determine whether any additional data will be necessary to evaluate its safety.

OPP's data requirements for registration (specified in "Pesticides Registration Proposed Data Requirements: Part 158") apply to both genetically engineered and non-engineered microbial pesticides. These requirements, which include product analysis, human safety, and ecological effects data, are adequate for the assessment of non-engineered pesticides. However, more extensive data or information may be necessary to evaluate genetically engineered pesticides. The regulation establishing these data requirements explicitly provides the necessary flexibility to require additional data if OPP determines a need for it.

In conclusion, FIFRA had authority to require that manufacturers provide adequate test data to establish the safety of their pesticide products, and the regulatory tools are sufficient for the program to regulate the use of genetically engineered pesticide products. OPP has already developed data requirements for microbial pesticides, and these will provide a first line of defense for the genetically engineered microbes. As we gain knowledge and experience from registering genetically engineered pesticides, it is likely that these data requirements will be modified or expanded.

III. TSCA

The question of how the Toxic Substances Control Act could be applied to biotechnology is less straightforward than the FIFRA case. However, our current view is that TSCA would provide authority to regulate recombinant DNA.

In 1982, OTS conducted a review of TSCA's potential role in biotechnology, resulting in a report which came to several conclusions. To begin with, commercial applications of biotechnology which would not be covered by other regulatory programs were nearing the commercial horizon. In addition, potential health and environmental concerns could be identified, but they would require extensive research before they could be considered well understood. Finally, the appropriate scope of TSCA's role was not clear, and needed to be defined from a scientific, a legal, and an administrative standpoint.

This report made it clear that oversight of biotechnology opens an enormously complex but important set of issues and responsibilities for TSCA. However, before we could begin to address these long-term issues, we had to answer the question of whether TSCA gives us authority to review these organisms before they are released and, if necessary, to regulate them. We believe that the answer is "yes"; now let me review the reasons for that conclusion.

The Toxic Substances Control Act was enacted in 1976. It is often referred to as the "gap-filling" environmental law, because its purpose is to regulate chemical substances in any application not specifically covered by other regulatory authorities.

The most significant section of TSCA which can be applied to biotechnology is Section 5. Section 5 is a powerful tool because it requires Agency review of new chemical substances prior to manufacture, before there is a problem and before the substances enter commerce and our environment. It applies specifically to new as opposed to existing substances.

Section 5 requires that any person who intends to manufacture a new chemical substance, other than for Research and Development, must submit a notice to EPA at least 90 days before manufacturing. Manufacturers are required to submit test data in their possession or control, descriptions of "known or reasonably ascertainable" test data, and "known or reasonably ascertainable" information on the chemical substance's identity, proposed uses, volume of production, by-products, workplace exposure, and manner of disposal. OTS reviews this information, and if there is a reasonable basis to conclude that commercial use will present unreasonable risks, we can regulate the chemical. We also have the option to prevent manufacture, or otherwise regulate the new chemical substance, pending the development of data, if there is insufficient information with which to make a reasoned evaluation. To do this, we must show that the substance may present unreasonable risks, or will result in significant human or environmental exposure. For example, if data on a new bioengineered organism were insufficient, we might regulate it by establishing that its ability to reproduce could result in significant exposure. In this case, controls would apply until the manufacturer provided data to allay EPA's concerns.

Thus, TSCA provides significant provisions for reviewing and regulating, if necessary, new chemical substances. But are the products of recombinant DNA technology subject to these provisions? We believe they are, because although the law is silent on this matter, the legal reasons supporting TSCA applicability appear compelling.

One significant fact is that the genetic material of life, DNA (deoxyribonucleic acid), clearly fits the legal definition of a "chemical substance" under TSCA. Using genetic engineering techniques to change DNA results in recombinant DNA, a new chemical substance. Therefore, recombinant DNA appears to be a new chemical substance under Section 5.

Another reason is the legislative history of TSCA, which shows that TSCA was created to fill the gaps where other environmental statutes leave off. Other statutes besides TSCA may apply, such as the Clean Water Act and the Clean Air Act, and OTS has begun to work with the offices which administer these acts to reach an understanding of their intended roles. However, to the extent other offices do not or cannot regulate biotechnology, the responsibility comes under TSCA's authority.

A third reason supporting TSCA's applicability in this area is that its comprehensive data gathering provisions allow us to monitor the production, use, and exposure of chemical substances. These provisions were created for the purpose of providing information on potentially harmful substances, and this authority may be very useful in the case of recombinant DNA.

Perhaps the most important argument in favor of TSCA oversight of biotechnology is that it is consistent with the traditional TSCA role of reviewing new chemical substances before they are put to widespread use. As mentioned above, this premanufacture review is one of the most powerful of TSCA's tools, and it could fill an important need in reviewing genetically engineered organisms before they are released in the general environment.

IV. IMPLEMENTATION ISSUES

Although TSCA and FIFRA provide authority to oversee recombinant DNA technology, there are numerous and very complex issues which EPA must address in implementing those authorities. These issues are significant, but not insurmountable.

Of primary importance is the fact that there is uncertainty with regard to which if any areas of recombinant DNA technology will require regulatory controls. The questions and concerns which can be raised are potentially serious, but they are still mostly speculative; clearly, more analysis is needed. EPA needs and plans to spend time working with industry and with the other governmental organizations to establish mechanisms for evaluating the true magnitude of these potential problems.

Secondly, because OPTS's role will be complementing the roles of other regulatory programs, a significant effort towards intra-governmental coordination and planning will be required in order to avoid overlapping responsibilities and to ensure that resources are used efficiently.

Another, internal consideration is that EPA's programs and staffs in general have little experience evaluating the safety of living organisms. Oversight of biotechnology is opening an entirely new area of responsibility for us. It will require extensive training of existing staff and recruitment of personnel with skills we have not previously required.

A serious technical problem, shared with other government agencies which are overseeing this area, is that there are almost no accepted methodologies for evaluating the safety of genetically engineered products. The risk assessment tools and data we have used for inanimate chemical substances will not apply in the case of organisms, and the requirements dveloped in OPP for non-engineered microbial pesticides may have to be modified for genetically engineered material. The list of needs is long, but at a minimum EPA must develop methodologies to evaluate environmental fate, human and environmental exposure, and potential environmental and health hazards of genetically engineered organisms. We are still several years away from having adequate testing methods and risk analysis techniques in any of these areas.

In conclusion, there are important problems and questions which EPA will have to overcome in order to provide regulatory oversight of recombinant DNA technologies. It seems clear that these issues will take significant time and resources to resolve, but we believe that the desired end result is achievable.

V. PLANS FOR THE FUTURE

I will conclude my discussion by describing to you the steps which EPA is initiating in the area of biotechnology. Our goal is to develop policies which are flexible and informed, and which ensure the safety of our health and our environment.

First, we have obtained funding commitments from our Office of Research and Development to develop the test methodologies which are critically needed for evaluating the safety of bioengineered products. The data requirements and testing methods we develop will be useful to the Office of Pesticide Programs, the Office of Toxic Substances, and other EPA programs which eventually become involved in evaluating the safety of bioengineered products. They will also be very important to industry, because it will ultimately be their responsibility to develop safe products.

As an aside, EPA's Office of Research and Development is also conducting research into potential environmental applications of biotechnology. Because the Committee requested information on recombinant DNA regulatory issues, I will not discuss these research endeavors today, but information on the research efforts of ORD can certainly be provided later if it would be of use.

Besides planning future research with the Office of Research and Development, OPTS has initiated an Agency-wide working group which is actively exploring the program issues and problems, and developing recommendations which will make the transition to these new responsibilities smoother. The Offices involved in this coordination effort include Pesticides and Toxic Substances, Drinking Water, Water Regulations and Standards, Solid Waste, Research and Development, and General Counsel.

Third, both OPP and OTS are coordinating their evolving biotechnology policies with other agencies which are regulating and conducting research in this field. To date, we have contacted the Food and Drug Administration, the Department of Agriculture, the National Institutes of Health, and the Occupational Safety and Health Administration to determine the status of their developing regulations and to learn from their experiences. We have also established contact with the National Institute for Occupational Safety and Health (NIOSH), the National Academy of Science (NAS), and the Office of Technology Assessment (OTA), each of which are publishing reports on environmental, legal or economic issues associated with genetic engineering. We hope to develop a workable consensus, perhaps including memoranda of understanding, on the appropriate roles of these various organizations. This coordination will also serve to avoid duplication of effort and unnecessary complexity for industry.

Besides working with other governmental groups, we are aggressively seeking public and industry participation in discussions relating to biotechnology. We have spoken with the Industrial Biotechnology Association, a 30-member industry trade association, and we plan to work with its members more extensively in the future. EPA has also entered into a cooperative agreement with the American Association for the Advancement of Science (AAAS) to sponsor a major symposium series on the scientific, economic, and legal aspects of biotechnology. The series began in November of 1982, and will continue through October of 1983. It has brought together world experts on biotechnology issues from the private sector, environmental groups, the press, and academia. Finally, we are using the Administrator's Toxic Substances Advisory Committee (ATSAC) as a mechanism to gain public participation and expert opinion. ATSAC was created specifically for the purpose of obtaining public input on major issues of importance to OTS and we have, and will continue, to use the ATSAC forum to discuss biotechnology issues and options.

In addition to these near-term goals and efforts, we are prepared to make the necessary commitments to educate existing staff and to recruit new expertise as it is needed. The Office of Pesticide Programs will clearly have increasing needs for expertise to review biotechnological pesticides and to develop more explicit procedures and requirements for evaluating them. In the Office of Toxic Substances, our needs for expertise may be even greater because TSCA's provisions for obtaining data to evaluate new chemicals place a larger burden of proof on EPA than do FIFRA's pesticide registration provisions. Although our resource needs depend on decisions which are still evolving, we are prepared to take a responsible role in evaluating, and to the extent necessary, controlling the products of biotechnology.

Thank you for your attention. I will be pleased to answer any questions you may have at this time.

Don R. Clay
Acting Assistant Administrator for Pesticides and Toxic Substances

The new Acting Assistant Administrator for Pesticides and Toxic Substances at the Environmental Protection Agency is Don R. Clay, a career administrator with a decade of service and a solid record of management at three federal agencies.

Since 1981, Mr. Clay has served as Director of the Office of Toxic Substances at EPA. Under his leadership, new strategies and initiatives have been developed in the "100 Day Report," a program designed to increase productivity and promote public health through chemical review.

Prior to EPA, Mr. Clay held management, planning and engineering posts at the Consummer Products Safety Commission and served as Deputy Assistant Commissioner for Planning and Evaluation at the Food and Drug Administration.

Don Clay is a registered professional engineer in his native Ohio and holds two degrees from Ohio State.

Mr. WALGREN. Thank you very much, Mr. Clay.

Dr. Kendrick?

STATEMENT OF DR. EDGAR L. KENDRICK, ACTING DEPUTY ASSISTANT SECRETARY FOR SCIENCE AND EDUCATION, U.S. DEPARTMENT OF AGRICULTURE, WASHINGTON, D.C.; ACCOMPANIED BY DR. SUE TOLIN, PROFESSOR OF PLANT PATHOLOGY, VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY, AND DR. TED HULLAR, ASSOCIATE DIRECTOR, NEW YORK AGRICULTURE EXPERIMENT STATION, CORNELL UNIVERSITY

Dr. KENDRICK. Thank you.

Mr. Chairman, members of the subcommittees, thank you for the opportunity to testify on the authority and jurisdiction of the U.S. Department of Agriculture in relation to the environmental impacts of genetic technology.

I am accompanied today by Dr. Sue Tolin, professor of plant pathology at Virginia Polytechnic Institute and State University and, also, associated with our Cooperative State Research Service as the Department's representative to the NIH Recombinant DNA Advisory Committee, and Dr. Ted Hullar, associate director, New York Agriculture Experiment Station, Cornell University.

Genetics have long been used by agricultural scientists to develop animals, plants, and microorganisms with improved traits for food, feed, and fiber production. New genetic technologies involving isolation and transfer of specific genes by recombinant DNA techniques offer tremendous potential for agriculture. These techniques will modify traditional processes for developing plants and animals for agriculture. Through various authorizations the Department supports research in cellular and molecular genetics and the many biotechnologies related to plant and animal production and protection.

Within the Department, recombinant DNA policy issues are addressed by the USDA Recombinant DNA Committee. Members of the committee are representatives of the agencies which support recombinant DNA research and include our Cooperative State Research Service, the State Agricultural Experiment Stations, the Agricultural Research Service, the Forest Service, the Office of Grants and Program Systems, and the Animal and Plant Health Inspection Service. The Department has also found it extremely valuable to have the Director of the Office of Recombinant DNA Activities of NIH as a member of the committee, as well as a representative for the National Science Foundation.

Additional policy committees regarding recombinant DNA and biotechnology in agriculture include the subcommittee of the experiment station committee on organization and policy, better known as ESCOP, for the State experiment stations, and the committee on biotechnology of the National Association of State Universities and Land Grant Colleges, NASULGC. Dr. Hullar, here with me today, is a member of that committee, and Dr. Tolin is a member of the ESCOP committee.

The Department has long officially supported the concept of a single set of standards, criteria, and principles for the conduct of

Government-funded recombinant DNA research in the United States, and with other Federal agencies concerned with the same issue, the Department has also supported the National Institutes of Health and its Recombinant DNA Committee, or RAC, as the lead agency for developing guidelines for conducting recombinant DNA research.

Although the RAC was originally formed to oversee potential human health and safety hazards of genetic engineering, issues relating to agriculturally important organisms and processes were addressed early on by the RAC. In formally addressing agricultural issues, the same rigorous scientific criteria and principles have been used.

The guidelines have generally been relaxed over the years, as Dr. Talbot has indicated and Dr. Hardy in his testimony, because no new hazards have been recognized from recombinant DNA molecules or from organisms containing recombinant DNA.

When an issue related to agriculture comes before the RAC, it is reviewed scientifically by the members of the RAC and by outside consultants with scientific expertise in the particular area. Following the review by the RAC, it is referred to the USDA Recombinant DNA Committee for final review and approval. Thus, the Department believes that the mechanisms are in place for review of special considerations that may be warranted by gentically engineered organisms.

Although a large share of the membership of the RAC is nonagriculturally oriented, their attitude and the attitude of the administrators of NIH assure agriculture that issues are adequately addressed by this body. Agriculture does, however, have special needs because the process of food and fiber production introduces organisms with all their genetic traits into the environment. Any possible changes to the environment are constantly reviewed by the agricultural science community as well as the private agribusiness sector and producers.

In the area of animal production, the USDA has authority under various laws, commonly referred to as animal quarantine and related laws, to regulate and take measures to prevent the introduction into the United States or the dissemination between States and territories of the United States of the contagion of, or any contagious infections or communicable disease of animals or poultry. The authority includes regulation of the movement of animals infected with or exposed to any communicable disease of livestock or poultry in interstate or foreign commerce. Thus, to the extent that any organisms containing recombinant DNA molecules could be classified as agents of diseases, they would be subject to regulation in accordance with provisions of the animal quarantine and related laws.

Under the authority of the Virus-Serum-Toxin Act, the Department licenses animal biological products which move in interstate commerce. All licensed products, and products under review for licensure, are subject to review for safety and other factors. Other authorities which might have a role in this area are the Federal Meat and Poultry Inspection Acts, which are concerned with providing wholesome and safe meat and poultry products to the public. Any meat or poultry products which are adulterated within the meaning of that term would, then, come under the prohibitions of these acts. If this adulteration were related to administration of products resulting from recombinant DNA research or to exposure to organisms containing recombinant DNA, then the provisions of these acts could have significance with respect to the area of recombinant DNA research.

In the production of plants, the Department has the authority to prevent the introduction into the United States of plant pests and to prevent the interstate movement of various plant pests not widely prevalent within and throughout the United States. Therefore, to the extent that organisms containing recombinant DNA molecules could be classified as plant pests, they would be subject to the regulation in accordance with the plant quarantine and related laws. The organisms would be subject to quarantine because they are pathogens, not because they contain recombinant DNA or have been genetically altered.

The U.S. Plant Variety Protection Act, originally passed in 1970, is administered through the Department's Agricultural Marketing Service. This act permits application for certificates of protection for novel varieties of sexually reproducing plants of certain species. Specific information is called for by the application, including a description of the variety and how it differs in identifiable morphological, physiological, or other characteristics from all prior varieties of public knowledge. It also includes a description of the geneology and of the procedure used in the development of the new variety. Thus, if recombinant DNA techniques are utilized, such procedures would be stated in the declaration of information concerning plant varieties protected under this act.

Microorganisms are certainly involved in agriculture, and in the event that genetically engineered micro-organisms are released into the environment for agriculturally beneficial purposes, these would be reviewed by the USDA and the NIH through the RAC, and perhaps also in cooperation with the Environmental Protection Agency as it fits under the Federal Insecticide, Fungicide, and Rodenticide Act, or FIFRA.

In summary, the Department has outlined its authorities for monitoring research, quarantine, and marketing of organisms developed through new genetic technologies. It does not, at present, see the need for new regulations.

Mr. Chairman, this completes my prepared statement. I will be pleased to respond to any questions you or the committee members may have.

[The prepared statement of Dr. Kendrick follows:]

STATEMENT OF
DR. EDGAR L. KENDRICK
ACTING DEPUTY ASSISTANT SECRETARY
FOR
SCIENCE AND EDUCATION
U. S. DEPARTMENT OF AGRICULTURE
BEFORE THE
SUBCOMMITTEE ON INVESTIGATION AND OVERSIGHT
OF THE
COMMITTEE ON SCIENCE AND TECHNOLOGY
U. S. HOUSE OF REPRESENTATIVES
JUNE 22, 1983

Mr. Chairman and Members of the Subcommittee, thank you for the opportunity to testify on the authority and jurisdiction of the U.S. Department of Agriculture in relation to the Environmental Impacts of Genetic Technology. I am accompanied today by Dr. Sue Tolin, Professor of Plant Pathology at Virginia Polytechnic Institute and State University and associated with our Cooperative State Research Service as the Department's representative to the NIH Recombinant DNA (deoxyribonucleic acid) Advisory Committee and Dr. Ted Hullar, Associate Director, New York Agriculture Experiment Station, Cornell University.

Genetics have long been used by agricultural scientists to develop animals, plants, and microorganisms with improved traits for food, feed, and fiber production. New genetic technologies involving isolation and transfer of specific genes by recombinant DNA techniques offer tremendous potential for agriculture. These techniques will modify traditional processes for developing plants and animals for agriculture. Through various authorizations the Department supports research in cellular and molecular genetics and the many biotechnologies related to plant and animal production and protection.

Within the Department, recombinant DNA policy issues are addressed by the USDA Recombinant DNA Committee. Members of the committee are representatives of the agencies which support recombinant DNA research and include CSRS and the State Agricultural Experiment Stations, ARS, Forest Service, and the Office of Grants and Program Systems, and the Animal and Plant Health Inspection Service. The Department has also found it extremely valuable to have the director of the Office of Recombinant DNA Activities of NIH as a member of the committee, as well as a representative for the National Science Foundation.

Additional policy committees regarding recombinant DNA and biotechnology in agriculture include the subcommittee of the Experiment Station Committee on Organization and Policy (ESCOP) for the State Experiment Stations, and the Committee on Biotechnology of the National Association of State Universities and Land Grant Colleges (NASULGC). Dr. Hullar, here with me today, is an member of that committee and Dr. Tolin is a member of the ESCOP committee.

The Department has long officially supported the concept of a single set of standards, criteria, and principles for the conduct of Government funded recombinant DNA research in the United States, and with other Federal Agencies concerned with the same issue, the Department has also supported the National Institutes of Health and its Recombinant DNA Committee (RAC) as the lead agency for developing guidelines for conducting recombinant DNA research. Although the RAC was initially formed to oversee potential human health and safety hazards of genetic engineering, issues relating to agriculturally important organisms and processes were addressed early on by the RAC. In formally addressing agricultural issues, the same rigourous scientific criteria and principles have been used. The guidelines have generally been relaxed over the years, as Dr. Talbot has indicated, because no new hazards have been recognized from recombinant DNA molecules or from organisms containing recombinant DNA. When an issue related to agriculture comes before the RAC it is reviewed scientifically by the members of the RAC and by outside consultants with scientific expertise in the particular area. Following the review by the RAC, it is referred to the USDA Recombinant DNA Committee for final review and approval. Thus the Department believes that the mechanisms are in place for review of special considerations that may be warranted by genetically engineered organisms.

Although a large share of the membership of the RAC is nonagriculturally oriented, their attitude, and the attitude of the administrators of NIH assures agriculture that issues are adequately addressed by this body. Agriculture does, however, have peculiar needs since the process of food and fiber production introduces organisms into new environments. Any possible changes to the environment are constantly reviewed by the agricultural science community as well as the private agribusiness sector and producers.

In the area of animal production, the USDA has authority under various laws, commonly referred to as Animal Quarantine and related Laws, to regulate and take measures to prevent the introduction into the United States or the dissemination between states and territories of the U.S. of the contagion of, or any contagious infections or communicable disease of animals or poultry. The authority includes regulation of the movement of animals infected with or exposed to any communicable disease of livestock or poultry in interstate or foreign commerce. Thus, to the extent that any organisms containing recombinant DNA molecules could be classified as agents of diseases, they would be subject to regulation in accordance with provisions of the Animal Quarantine and related laws.

Under the authority of the Virus-Serum-Toxin Act, the Department licenses animal biological products which move in interstate commerce. All licensed products, and products under review for licensure, are subject to review for safety and other factors. Other authorities which might have a role in this area are the Federal Meat and Poultry Inspection Acts, which are concerned with providing wholesome and safe meat and poultry products to the public. Any meat or poultry products which are adulterated within the meaning of that term would come under the prohibitions of these Acts. If this adulteration were related to administration of products resulting from recombinant DNA research or to exposure to organisms containing recombinant DNA, then the provisions of these acts could have significance with respect to the area of recombinant DNA research.

In the production of plants, the Department has the authority to prevent the introduction into the United States of plant pests and to prevent the interstate movement of various plant pests not widely prevalent within and throughout the United States. Therefore, to the extent that organisms containing recombinant DNA molecules could be classified as plant pests, they would be subject to regulation in accordance with the Plant Quarantine and related laws. The organisms would be subject to quarantine because they are pathogens, not because they contain recombinant DNA or have been genetically altered.

The United States Plant Variety Protection Act, originally passed in 1970, is administered through the Department's Agricultural Marketing Service. This Act permits application for certificates of protection for novel varieties of sexually reproducing plants of certain species. Specific information is called for by the application, including a description of the variety and how it differs in identifiable morphological, physiological or other characteristics from all prior varieties of public knowledge. It also includes a description of the geneology and of the procedure used in the development of the new variety. Thus, if recombinant DNA techniques are utilized, such procedures would be stated in the declaration of information concerning plant varieties protected under this Act.

Microorganisms are certainly involved in agriculture, and in the event that genetically engineered microorganisms are released into the environment for agriculturally beneficial purposes, these would be reviewed by USDA and NIH through the RAC, and perhaps also in cooperation with the Environmental Protection Agency as it fits under the Federal Insecticide, Fungicide, and Rodenticide Act.

In summary, the Department has outlined its authorities for monitoring research, quarantine, and marketing of organisms developed through new genetic technologies. It does not, at present, see the need for new regulations.

Mr. Chairman, this completes my prepared statement. I will be pleased to respond to any questions you may have.

VITA

Edgar L. Kendrick

EDUCATION

University of California Berkeley, California	*Botany* *(Minor in Genetics)*	B.A.	1960
University of Wisconsin	*Plant Pathology*	Ph.D.	1954

EMPLOYMENT HISTORY

1953–1965	*Research Plant Pathologist, Crops Research Division, ARS, USDA, Pullman, Washington*
1965–1968	*Assistant Branch Chief, Cereal Crops Research, Crops Research Division, ARS, USDA, Beltsville, Maryland*
1968–1972	*Assistant Director, Plant Science Research Division, ARS, USDA, Beltsville, Maryland*
1972–1976	*Area Director, Arizona-New Mexico, ARS, USDA, Western Region, Tucson, Arizona*
1976–1978	*Associate Administrator, Southern Region, Science and Education Administration, Federal Research, USDA, New Orleans, Louisiana*
1978–1983	*Regional Administrator, Southern Region, Agricultural Research Service, USDA, New Orleans, Louisiana*
9/82–Present	*Acting Deputy Assistant Secretary, Science and Education, USDA, Washington, D.C.*
7/83–Present	*Director, Office of Grants and Program Systems, Science and Education, USDA, Washington, D.C.*

AWARDS

USDA Unit Award for Superior Service. 1960

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PROFESSIONAL ACTIVITIES

Offices: *Chairman, 1971-74, and Director-at-Large, 1975-present, Board of Trustees, American Type Culture Collection; Treasurer, American Phytopathological Society, 1976-1982*

Membership: *American Phytopathological Society, American Type Culture Collection, Sigma Xi and Phi Sigma Honor Societies, Federal Executive Institute Alumni Association, Federal Executive Institute Alumni Association, Federal Executive and Professional Association.*

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September 1983

Mr. **Walgren**. Thank you very much, Dr. Kendrick.

I would think it probably best to limit this somewhat at this point.

Let me just ask Dr. Talbot, what is the composition of the RAC Plant Working Group? It has been mentioned that it does not include ecologists. Could you perhaps confirm that and then submit a summary of its composition to the committee?

Dr. **Talbot**. Right. The full RAC does not include an ecologist. In addition to the full RAC, we now have a RAC Plant Working Group, which also does not contain an ecologist. I will be glad to provide for the record the names and affiliations of both the full RAC and the RAC Plant Working Group.

[Information to be provided for the record follows:]

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Mr. **Walgren**. Does EPA have a formal position on whether or not TSCA covers genetically changed material?

Mr. **Clay**. The testimony prepared today was cleared by the official EPA clearance process. I have had signoffs by the various parts of the agency. It was also approved by the Office of Management and Budget before coming.

To the degree that we at this time suggest that it has, although, as was discussed earlier, it will probably be litigated, the agency position is that it does cover.

Mr. **Walgren**. I see questions as to how that litigation comes on. Mr. MacKay?

Mr. **MacKay**. It seems to me that the panels previous to you are not aware that EPA is taking this position. What I want to know is, since nobody is aware of it and you have not asserted it yet, how do we ever get to a point where we find out the answer? In other words, how are we going to take this into the real world?

Mr. **Clay**. What we are doing, we are actually planning the effort on what we are going to be doing. We have in late 1982 started in the public forum the Administrator's Advisory Committee on Toxic Substances discussing the idea of doing it. As for their opinion, it is generally that we do, in fact, have jurisdiction.

We are planning as if we do have jurisdiction, but our indications are that under TSCA we are several years away before anything is coming down the road that would require regulation. TSCA does exempt things that are under research and development from coverage by TSCA under section 5(h)(3). We are several years away before anything comes, before anybody knows for sure.

When they come, and I suspect people will come and talk to us about it, much as they did with the synfuels, we will enter a discussion period. It will be our position that it is covered, and when they try to make them for commercial purposes they should submit a PMN.

Mr. **Walgren**. However, it does not apply at all to the research and development handling at that point.

Mr. **MacKay**. If there is gap, then the gap is in the possible introduction of materials into the environment during research, which you do not even contend you have——

Mr. **Clay**. No. Congress specifically excluded that under section 5(h)(3).

[The following letter was subsequently received for the record:]

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Honorable Albert Gore, Jr.
Chairman, Subcommittee on Investigations and Oversight
Committee on Science and Technology
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

Thank you for the opportunity to testify at your June 22nd hearing on the environmental implications of biotechnology. I appreciated the chance to explain the work of the Office of Pesticides and Toxic Substances in reviewing recombinant DNA technology, and to hear the opinions of the other experts who testified at the hearing.

I would like to clarify one statement I made in response to a question asked of me at that hearing. The question was whether the Toxic Substances Control Act (TSCA) can be used to oversee or regulate biotechnology research. I replied that research is explicitly excluded from premanufacture notice (PMN) requirements under section 5(h)(3) of TSCA. However, the exclusion is conditioned by the requirement that "all persons engaged in ... experimentation, research, or analysis for a manufacturer or processor ...(must be) notified ... of any risk to health which the manufacturer, processor or the Administrator has reason to believe may be associated with (the) chemical substance." Thus, the Environmental Protection Agency (EPA) could require that employees engaged in the Research and Development (R&D) be notified of risks associated with their activities.

Other provisions of TSCA would have to be used for EPA to evaluate and regulate biotechnology R&D. For example, under section 4 of TSCA, EPA could require companies to test R&D substances for health and environmental effects, if it could find that the substances "may present an unreasonable risk of injury to health or the environment," and that currently available data or experience are insufficient. Section 6 could be used to regulate R&D activities if EPA could make the finding that the substance "presents an unreasonable risk." Lastly, section 8 of TSCA provides authority to collect information from manufacturers and processors of chemical substances. In the case of R&D substances, EPA would have to show that the information to be collected was "necessary for the effective enforcement" of the Act. In conclusion, EPA clearly has authority under certain circumstances to regulate biotechnology R&D.

At this time, however, there are several reasons to support a continuance of the current situation, in which the National Institutes of Health Recombinant DNA Advisory Committee (RAC) reviews the safety of all recombinant DNA research. First, there are advantages to having a single set of federal standards, particularly when the risks of concern are fairly similar as they are in the case of research and development activities. Second, the RAC has the appropriate general expertise to oversee scientific research, and they have recently appointed an ecologist to their committee, thus broadening their expertise in the important area of environmental concerns. Finally, they have extensive experience, and they appear to be doing a good job. Nonetheless, I agree with the concern expressed by you and your colleagues regarding the RAC's lack of enforcement authority, and I believe that if there proves to be a problem with enforceability of regulations in the future, EPA could use its authority to help regulate the portion of research activity which falls under TSCA jurisdiction.

I hope this clarifies my response to your question. Please let me know if I may be of further assistance.

Sincerely yours,

(SIGNED) DON R. CLAY

Don R. Clay
Acting Assistant Administrator
Office of Pesticide and Toxic Substances

cc: Honorable Doug Walgren

Mr. WALGREN. I guess the question comes as to how completely we can rely on TSCA if it does not cover that part of the process at all.

Let me also understand the difference between the Fungicide Act and the Toxic Substance Act with respect to a demonstration of safety. Does it exist in one and not in the other? Is that the point?

Mr. CLAY. No; that is not exactly true. FIFRA is a registration process where you have to satisfy the requirements, which we have published in part 158 for microbial agents, what we think we are going to need, but we also allow the flexibility.

Under FIFRA, we have to have the data that we have before we will register it, and you have to have it registered before you can use it as a commercial application or receive an experimental use permit.

Under TSCA, the burden is more on the Government to prove there is a problem. TSCA is a notification scheme where you must notify the agency 90 days in advance to manufacture a new chemical substance, which is defined as something not already in existence or on the inventory. In that case what we would have to do, we would have to make a finding that there would be a possibility of significant risk in order to do it, but we think we can do so. We either have significant risk or we have exposure to do that, and then require the testing that way. There is more burden on the agency under TSCA than there is FIFRA. No question about that. However, we think that the TSCA is designed as a very flexible statute and that we have flexibility to insure the testing is done.

Of course, part of the problem is with TSCA or FIFRA or any piece of legislation that you might have to control the difficulty of doing the risk assessments, which you talked about earlier today, which is independent of what statute you choose to do it.

Mr. WALGREN. I see.

Mr. MACKAY. I have just one more question.

Dr. Talbot, your testimony indicated that a number of legislative proposals came up in 1977 and 1978 to make the guidelines mandatory.

Dr. TALBOT. Yes.

Mr. MACKAY. Then apparently that has sort of drifted away.

Dr. TALBOT. It has drifted away. There have been no bills introduced in the last Congress nor this Congress.

Mr. MACKAY. What would be your reaction to that? Do you think that would be an appropriate response, not overreacting?

Dr. TALBOT. I think the general response in the public back in 1977 was fear about this new technology. That fear has largely gone away, and people feel that the controls are adequate. Therefore, the pressure for national legislation has quieted down.

Mr. MACKAY. Do you feel that the controls are adequate?

Dr. TALBOT. Yes; I do.

Mr. MACKAY. Thank you, Mr. Chairman.

Mr. WALGREN. It certainly is interesting testimony. I could not help but notice they used the word "recall" in the last panel. I suppose language carries implicit messages. Likening the recall in this area to what we associate with recall in terms of automobiles and the like is not exactly the same thing. I do want to personally say that I hope we approach this area with some great caution.

I think we have some interesting comments by the witnesses that do underscore the lack of the comprehensive coverage of the guidelines and general support for comprehensive coverage of the guidelines. How the committee will respond to that will be interesting to see.

We thank you very much for your testimony.

With that, the hearing is adjourned.

[Whereupon, at 1:05 p.m., the hearing adjourned.]

APPENDIX A

ORNL/TM-8473

Contract No. W-7405-eng-26

SPREAD OF ORGANISMS WITH NOVEL GENOTYPES: THOUGHTS FROM AN ECOLOGICAL PERSPECTIVE

F. E. Sharples

ENVIRONMENTAL SCIENCES DIVISION
Publication No. 2040

Date Published: October 1982

NOTICE This document contains information of a preliminary nature. It is subject to revision or correction and therefore does not represent a final report.

OAK RIDGE NATIONAL LABORATORY
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operated by
UNION CARBIDE CORPORATION
for the
DEPARTMENT OF ENERGY

ACKNOWLEDGMENTS

This report was prepared during the author's tenure as an Environmental Science and Engineering Fellow during the summer of 1981. The Environmental Science and Engineering Fellowship program was sponsored by the U.S. Environmental Protection Agency (EPA) and coordinated by the American Association for the Advancement of Science. The work was performed while in residence at the headquarters of EPA in Washington, D.C.

Although the research described in this report has been funded wholly or in part by the United States Environmental Protection Agency (EPA), it has not been subjected to EPA review and therefore does not necessarily reflect the views of EPA and no official endorsement should be inferred.

ABSTRACT

SHARPLES, F. E. 1982. Spread of organisms with novel genotypes: Thoughts from an ecological perspective. ORNL/TM-8473. Oak Ridge National Laboratory, Oak Ridge, Tennessee. 58 pp.

One category of objection to the release of organisms produced by genetic engineering is based on the fear that such organisms may persist in the environment and damage existing ecosystems. An assessment of such environmental risk thus involves an ecological question analogous to the introduction of exotic species which has been known to produce serious ecological disruptions. A review of the literature on exotic introductions reveals, however, that foreign species do not invariably produce adverse changes. Ecologists believe that only a fraction of immigrating species actually produces ecological dislocation while the majority probably fail to penetrate existing biotic assemblages. Stressed or simplified environments are, however, more vulnerable to successful invasion. Unfortunately, because very little information has ever been collected to document the number or causes of failed introductions, it is impossible to quantify the probability that any introduced species will or will not cause serious disturbance purely on the basis of historical evidence.

INTRODUCTION

Much of the controversy on the health and safety risks of recombinant DNA (rDNA) technology has now abated. The National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Modecules have been in place since June 1976. These guidelines have imposed restrictions on the kinds of experiments that may be performed and have specified levels of physical and biological containment for rDNA experiments that are carried out.

The guidelines have never, however, addressed the full spectrum of issues related to genetic engineering. Three important points are relevant to the discussion in this document:

1. The guidelines are only legally binding on researchers who receive NIH funding for rDNA research. Compliance by other federal agencies and industry is voluntary.
2. The guidelines address only the rDNA technique itself. Other methods of genetic "engineering," such as cell fusion, transformation, and treatment with mutagens, can also produce organisms with unusual genotypes but are not subject to regulatory oversight.
3. The guidelines avoid resolving the issue of environmental (as opposed to health and laboratory safety) risks by prohibiting release of engineered organisms into the environment. Microbial technologies for metal leaching and recovery, enhanced oil recovery, and pollution control provide instances where environmental release may be necessary and desirable. Adherence

to a prohibition on release would obviously preclude such potentially beneficial uses of organisms "improved" by the rDNA technique.

Why Should the Environmental Protection Agency Be Interested in Genetic Engineering?

There are two major routes by which EPA could become involved in decision-making related to genetic engineering.

First, microbial methods of detoxification or degradation offer promise as a means of dealing with intractable pollutants. The Environmental Protection Agency (EPA) already supports research on microbial development for this purpose. The use of the rDNA technique could greatly accelerate this development. Prohibition of environmental release could, however, hinder implementation of a control technology utilizing a recombinant organism.

Second, and perhaps more important, is the potential need for EPA to regulate environmental uses of genetically engineered organisms under several of the federal statutes defining the Agency's mission. Possible sources of regulatory authority include (OTA 1981):

1. The Federal Insecticide, Fungicide and Rodenticide Act (7 U.S.C. 136 et seq.).

The statute requires hazard testing before registration of pesticides. The EPA's proposed "Guidelines for Registering Pesticides in the United States, Subpart M" cover the "biorational" (biochemical and microbial) pest control agents. These guidelines already distinguish between microbial agents produced by the rDNA technique and those produced in other ways and require higher levels of hazard testing for recombinant organisms.

2. The Toxic Substances Control Act (TSCA) (15 U.S.C. 2601 et seq.).

"Chemical substance" is defined in TSCA as "any organic or inorganic substance of a particular molecular identity including any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature . . . ."

Under TSCA, EPA may prohibit or restrict the use of a chemical which may present "an unreasonable risk" to health or the environment, particularly if data are insufficient to evaluate the chemical's effects. TSCA would provide the broadest authority to regulate rDNA organisms if EPA were to interpret the definition of chemical substance to include the DNA in living organisms. There has been disagreement on this interpretation in the past (OTA 1981).

3. The Marine Protection, Research and Sanctuaries Act (33 U.S.C. 1401 et seq.).

This act prohibits ocean dumping without an EPA permit. It is applicable to any material (including biological materials) which would "degrade or endanger human health, welfare, or amenities, or the marine environment, ecological systems, or economic potentialities."

4. The Clean Water Act of 1977 (33 U.S.C. 1251 et seq.), the Resource Conservation and Recovery Act of 1976 (42 U.S.C. 6901 et seq.), and the Clean Air Act (42 U.S.C. 7401 et seq.).

These statutes collectively regulate discharge of pollutants and hazardous wastes and are applicable to biological materials (e.g., bacterial aerosols).

The Issue of Environmental Risk

Very little effort has been devoted to assessing the likelihood of a genetically engineered organism becoming established in the environment and causing ecological damage. A report on the impacts of applied genetics by the Office of Technology Assessment (OTA) has, however, raised several points in this regard (OTA 1981). First, it cited examples of ecological damage produced by introduction of exotic organisms into new environments. Second, it posed the question of whether such examples provide a relevant analogy for assessing the potential dangers of organisms with man-made genotypes. Finally, it asked specifically whether minor genetic differences in such an organism could be equated with a totally foreign species due to its smaller percentage of novel genes. The OTA discussion therefore provided a starting point for the present investigation. This report is structured to answer the following interrelated questions:

1. Can an assessment of the probability that a novel organism will become established and cause ecological damage be made, based on the knowledge that is already available in the ecological literature?

2. How different must an organism's genome be to change its role in the environment?
3. In general terms, how relevant is available ecological data to the question of environmental risk?

These questions should be addressed primarily to allow a judgment of whether existing information is sufficient to assess the environmental risks associated with recombinant organisms and to help define what new work, if any, is needed. The method used to address these questions was to review literature on introduced species and on development of genetic resistance to antibiotics and pesticides. The latter subject was included because it provides a parallel with genetic engineering in that genetic changes conferring resistance have occurred as a result of human activity.

THE INTRODUCTION OF EXOTIC SPECIES

The literature on introduced species covers many hundreds of cases. The large size and diversity of this literature is some indication of the frequency with which exotic introduction has occurred. Much of the information available, however, is anecdotal and lacking in detail. Although recent references on the basic biology of some introduced species are available, the literature directed specifically at analysis of their ecological impacts as exotics is rather dated. Little new information on the ecological role of exotics has been developed recently.

The following discussions provide examples of general principles involved with exotic introductions. Given limited time, it was certainly not possible to cover all known cases of exotic introduction or even to always trace the selected cases back to primary sources. Thus, this presentation does not claim to be complete or exhaustive; it is intended to provide sufficient information to support qualitative generalizations made in the summary.

Microorganisms

The significance of the importation of foreign microorganisms has been particularly obvious whenever the invasion has involved a pathogen. The world-wide occurrence of bubonic plague, the periodic appearance of foot-and-mouth disease in the United States, and the disappearance of our native American chestnuts are all indications of the movement of nonnative microorganisms into new environments. Because the emphasis of this document is primarily on environmental, rather than health, effects, it is appropriate to consider the impacts of a nonhuman pathogen on an ecological system.

In the early 20th century, the fungus Endothia parasitica was brought to the United States on nursery plants from Asia. This organism came to be known as the "chestnut blight." In Asia, the parasitic fungus does little harm to its natural host chestnuts (Elton 1958). Similarly, the American chestnut, Castanea dentata, carried two native species of Endothia that were nonpathogenic. But the Asian fungus was extremely lethal to the American tree which had no immunity to it. The American chestnut had almost completely died out by 1950.

Shugart and West (1977) attempted to determine the nature of changes in forest structure and dynamics which occurred with the sudden removal of the chestnut. The species was one of the most important in the canopy of the Appalachian oak-chestnut forest. It apparently had the ability to do well over a wide variety of soil conditions, in almost all forest types, any slope aspect, and at all elevations ranging from sea level to 1500 m. Quantitative data on the pre-settlement forest of the southern Appalachians are scarce, but the chestnut was undoubtedly one of the six most important tree species. It tended to reproduce vegetatively and was fast growing and shade tolerant. Shugart and West (1977), therefore, believe that the chestnut was important in maintaining a higher rate of stand recovery following disturbance. Utilizing modeling techniques, they showed that although the number of trees tends to be similar in pre- and post-chestnut blight forests, the functioning of the forest as well as the species composition has been significantly altered. Forest leaf areas appear to be shifted to slightly lower values and the dynamics of stand biomass values are different. Both of these differences represent changes in the functional behavior of forest ecosystems that one might logically expect to have repercussions on the element cycles of forests, on the gaseous exchange rates of forest canopies, and on forest ecosystem production rates. A greater variation in biomass through time was consistently observed when single species dynamics without chestnut were compared to the case with chestnut present. This increase in variability may be indicative of destabilized community dynamics in the absence of chestnut. These effects are in addition to those associated with loss of an important mast-producing tree for wildlife and as a timber resource. In this case, the introduction of an exotic organism produced an ecological perturbation of great magnitude, i.e., the disappearance of an entire species.

Of course, not all introduced microorganisms are pathogens, and the degree to which ecological modifications have been wrought by non-disease producing exotics will probably never be known. D. Weber (personal communication, 1981) of the U.S. Department of Agriculture, Beltsville, reported that one of the most common and successful strains of the nitrogen-fixing symbiont Rhizobium japonicum infecting soybeans in the United States is the same serological type as the dominant strain in China. He infers that the bacterium was probably introduced in soil or plant material early in this century and has been holding its own in competition with native strains ever since. Nothing is known about the effects the introduced strain may have had on indigenous bacteria.

An important point that needs to be made here is that microorganisms are integral components of ecosystems just as higher organisms are. Microbes compete, prey on each other, and modify each other's environment chemically and physically. Stable climax communities of microorganisms evolve by the same processes of selection and succession as do communities of higher organisms. Microbial climax communities are usually extremely resistant to invasion by introduced aliens (Alexander 1971). For example, despite continual additions of diseased tissue, dead bodies, and excrement to soil, or sewage and agricultural debris to water, it is rare for organisms introduced with these materials to persist as permanent residents. An established microbial community will usually react in such a way as to reject any aliens or hold their abundance in check.

Indigenous microflora are not, however, always impenetrable. Environmental perturbation can often allow new species to become dominants. Among the kinds of stresses shown to bring about ecological upsets are nutrients added by man, toxic pollutants introduced into water, and chemical or physical treatments leading to elimination of large numbers of organisms (Alexander 1971). "The use of antimicrobial agents in medicine, veterinary practice, and agriculture or the release of toxic materials into flowing water constitutes an ecological perturbation that destroys the original homeostatic mechanisms and commonly establishes conditions suitable for the dramatic rise in numbers of a species hitherto uncommon in the locality."

Plants

Of all introduced organisms, plants are the most economically important. In the United States, most of our grains, vegetables, and fruits are of foreign origin (Courtenay 1978). Anderson (1969) states, in fact, that the only food crop species of world status to originate and be domesticated within U.S. boundaries is the sunflower. All our other crops were originally either Asiatic or came north from tropical parts of the New World. If an examination of the role of exotics focused only on agricultural plants, the conclusions one would draw about the environmental effects of introductions would be almost entirely positive. The introduced crops have been minimally disruptive to native plant and animal communities (Courtenay 1978) and for the most part are completely dependent on man for their survival. Bates (1956) gives three reasons for this dependence. Some crop species have lost the capacity to produce viable seed and must be propagated by man vegetatively (e.g., bananas and bread fruit). Others produce viable seed, but in such a way as to require human removal and planting (e.g., maize). For most crops, however, it is merely assumed that their failure to become established in the wild is due to their inability to compete. Most introduced plants can only survive in environments in which man-made alterations are maintained by continual disturbance, creating "open" habitats (Anderson 1956, 1969).

Still, the relationships between the major crops and their weedy wild relatives are not well understood. It is known that some crops were definitely derived from weeds, e.g., rye (Anderson 1956) and that the development of our modern cultivated varieties sometimes involved hybridizations between crop plants and weeds. Anderson (1969) gives an account of the origin of the bread wheats which entails hybridization and polyploidy between three, and possibly four, separate genera. This process can, of course, go in both directions. Anderson also mentions tetraploid weedy rices which may be derivatives of the diploid domesticated species. On balance, however, there are few references to "escape" of cultivated species. The only one Anderson mentions is bamboo which apparently spread from cultivation to cover whole mountainsides on Caribbean islands. And although vast numbers of horticultural species are imported, only a fraction have apparently ever become problem introductions. Bates (1956), for example, reported that a catalogue of species subject to deliberate horticultural introduction in 1941 listed 19,600 species in 2,700 genera. Courtenay (1978) also cites a report in which the number of imported varieties and species tested for potential introduction by the U.S. Office of Foreign Seed and Plant Introduction was given as 200,000. George White, Plant Introduction Officer at the U.S. Department of Agriculture, Beltsville, Maryland, knows of no case in which an exotic imported in the program has ever produced an ecological disruption (G. White, personal communication, 1981).

This is not to say that introduced plants have never become widespread nor had substantial ecological impact. Major modifications of regional floras by foreign invaders have certainly occurred. Excellent examples are provided by grasses in California and the eastern United States.

The introduction of exotic plants into California began with the arrival of the Spanish missionaries and explorers in the 18th century (Raven 1977). Today, the state's introduced flora numbers 654 species in 320 genera, with grasses representing roughly 20% of the total. Apparently, introductions of annual grasses were not deliberate. Seeds probably arrived in livestock feeds, packing materials, and in the digestive tracts of domestic animals (Heady 1977).

Clark (1956) states that the original appearance of California's grasslands is "not a matter of historic record." It is generally assumed, however, that most of the Central Valley, the coastal prairie, and the lower slopes of the Sierra Nevada had a dominant cover of perennial bunch grasses. Today, even in areas which have remained unplowed, the dominant species are introduced annuals. The invaders have included grass species of limited palatability for cattle (e.g., *Bromus rigidus*, ripgut, and *Hordeum murinum*, foxtail) and also other noxious plants such as klamath weed (*Hypericum perforatum*) and Russian thistle (*Salsala kali*, tumbleweed). These annuals are exotic not only to California but also to the North American continent (Clark 1956). Originating in southern Europe, they were widely adapted to a Mediterranean climate, to grazing, and to competition with perennials (Heady 1977). They were thus well equipped to become established in California. It is not clear to what extent livestock grazing pressure facilitated the nearly complete replacement of the native perennials. Some authors believe this would have occurred anyway due to the competitive ability of the aggressive weedy annuals. In any case, these are now so firmly extrenched that they cannot be removed or even, perhaps, reduced (Heady 1977). Fortunately, as Clark pointed out, the remaining grassland plays a very small part in the overall economic structure of California.

As is often the case in the literature on introduced species, a similar event elsewhere has had a completely different economic outcome. According to Curtis (1956), the combination of grazing disturbance with introduction of an alien species more clearly accounts for a dramatic, although today largely unrecognized, modification in our eastern grasslands. Grazing by livestock produces continuous reduction of photosynthetic leaf area and a decrease in the storage of nutrient reserves in tall erect grasses. Reproductive capability is thus sacrificed to the need for continuous vegetative growth. Grasses such as bluestems (Andropogon sp.), Indian grass (Sorghastrum nutans), and switch grass (Panicum virgatum) are eventually weakened and replaced by species with recumbent leaf forms. These escape destruction by cattle, which normally do not graze closely, and in the absence of competition from the former upright dominants, become "increasers." In eastern North America, the most important "increaser" has been the familiar Kentucky bluegrass (Poa pratensis). Although an introduced species, P. pratensis is not an annual, is highly palatable, and does not require bare ground to get established. It is fortuitous that this vigorous alien has come to dominate most of the unimproved pasture in the eastern half of the continent. Interestingly, P. pratensis has been accompanied by an assemblage of other European grasses and forbs (e.g., dandelion, white clover, ox-eye daisy, quack grass, and timothy) such that our eastern pastures are inhabited by a largely exotic flora which replicates a man-made community very widespread in Europe.

Insects

Probably the most unqualified mistakes in species introductions are those involving insects. Elton (1958) reported that nearly half of the roughly 180 major plant pests of the United States have been imported. Exotic insects are notorious not only as agricultural and forest pests but also as vectors of disease introduction. On the other hand, deliberate and carefully planned efforts to establish alien animals for pest control purposes more often involve insects than any other taxonomic group.

Pest control with insect counterpests often involves species which specialize in feeding on or attacking a single target or prey item. Other criteria that counterpests should typically meet are: (1) that they not be vectors of disease; (2) that their presence produce minimal perturbation in the invaded community; and (3) that they be capable of effective control of the target pest (Paine and Zaret 1975). Occasional outstanding successes are on record. In Australia, for example, a South American moth (*Cactoblastis cactorum*) is reported as having freed 50 million acres (2 0 million hectares) of land from the dominance of the introduced prickly pear cactus (*Opuntia inermis*) (Courtenay 1978). Also in Australia, the importation of African dung beetles solved a problem of rapidly accumulating dung pads produced by high densities of cattle and sheep. It was estimated that 6 million acres (2.4 million hectares) of Australian pastureland per year were encumbered by persistent dung pads produced at the rate of some 300 million per day (Paine and Zaret 1975). In the absence of native dung destroying agents, the problem had become formidable. One species of dung beetle is now broadly distributed, cow dung disappears in 48 h, and a dung-inhabiting fly which had also become a problem has been reduced.

Such sterling examples of ecological complementarity are not really typical, however. Many counterpests fail to become established, and many more become established but fail to produce control of the target pest (Elton 1958). Our understanding of the reasons for these failures is, unfortunately, no better than our ability to predict the outcome of a successful introduction. Goeden and Louda (1976) reviewed the recent literature on phytophagous insects imported for weed control in an effort to identify how large a role is played by biotic factors in preventing establishment. Their conclusions were as follows. Predation by indigenous insects on phytophagous pest control agents varies in its outcome from outright prevention of establishment to no appreciable effect on the imported insect at all. "Therefore, this range of results provides no basis for predicting the influence of predation on the outcome of future colonization of phytophagous insects for the biological control of weeds other than to allow the presumption that predation is likely to occur" (Goeden and Louda 1976). No failure to establish a colonizing species could be directly attributed to parasitoids. "Instead, if parasitoids exerted any influence at all, this usually involved successfully colonized biological control agents." Furthermore, where parasitoids were implicated, they were sometimes organisms previously introduced for control of other insect pests. Finally, the effects of disease on imported phytophagous insects appeared to be less severe than those of predation, and often involved only populations pre-disposed to disease by overcrowding, depleted food supplies, or other expressions of intraspecific competition. In short, Goeden and Louda (1976) concluded that the question of the significance of biotic factors in the failure or reduced effectiveness of weed control agents remains unanswered.

If it is not already obvious, the establishment of a new organism is not often a simple matter. "The number of insects that become established in new regions through human agency. . .is but a small fraction of the species that are constantly being moved about" (Bates 1956). Insects are, however, extremely easy to transport accidentally. Elton (1958) recounts the results of an ecological survey once performed by a tropical entomologist to amuse himself while traveling aboard a rice ship from Trinidad to Manila. Altogether, he found 41 species of travellers, most of them insects. At least one species, Tribolium castaneum, a pest of stored grains, accompanied him to his hotel room in his luggage. Despite elaborate provisions for inspection and quarantine, it is likely that some insects will still get by whatever barriers human beings erect to keep them out. It seems likely, for example, that the mode of entry of the South American fire ants (Solenopsis invicta and S. richteri) will never be determined (Lofgren et al. 1975). The arrival of these nuisance species in the southeastern United States cannot be associated with any specific imported cargo.

In other cases, of course, we know exactly how a pest arrived. Perhaps the most famous case of an intentional import and an accidental release is that of the gypsy moth. This animal is such a classic example of a successful introduced species that it is worth describing more fully.

In 1868 or 1869, Leopold Trouvelot, a French astronomer employed at the Harvard Observatory, returned from Europe with some eggs of the European moth, Lymantria dispar (Elton 1958). He was apparently trying to breed a disease-resistant silk worm in his house in the Boston suburb of Medford, Massachusetts. Trouvelot's motives were well intentioned, and having recognized the omnivorous habits of his animals, he notified the authorities when some of them somehow escaped (Swain 1981). By 1880, however, the gypsy moth had prospered and occupied 500 square miles (1300 km^2), eventually spreading throughout New England. In the 1940's, it was reported that a barrier zone had been successfully established to keep the moth from dispersing west of the Hudson River and that it had reached the limits of its distribution (Brown and Sheals 1944). In the 1970's, its range was still expanding, and at an accelerated rate (Leonard 1974). An estimated 10 million acres (4 million hectares) of trees were defoliated by the moth in 1981. The real limits to its spread are likely to depend on climatic factors and availability of host plants (Leonard 1974). It can feed, however, on 450 to 500 different plant species and has managed to adapt behaviorally to certain adverse conditions in its environment. For example, temperatures below -25°C are lethal to overwintering eggs. Female gypsy moths, however, have begun to deposit their egg masses nearer to the ground where they are protected by the insulation of snow. This contributes greatly to increased survival in more northern climates.

Other factors that have contributed to the moth's success are its fecundity and dispersal capabilities. Newly hatched larvae are well suited for passive dispersal by wind, and their behavior facilitates this mechanism. Larvae which do not reach a suitable food source after hatching are very active. They move upwards to the tree tops and, if air is blown over them, they arch and release their attachment from the surface to be dispersed by the wind. The gypsy moth females also respond to increasing population densities by producing lesser food reserves for the eggs. Larvae that hatch from these eggs remain active longer before feeding, and during this longer activity time, they are even more readily dispersed by wind (Leonard 1974). Interestingly, man also facilitates the spread of this pest by transporting insects from infested areas on vehicles. Thus, man is "primarily responsible for long-range dispersal" (Leonard 1974).

The degree of permanent damage caused by this animal is somewhat open to question. Brown and Sheals (1944) reported that mortality of defoliated trees was not great because outbreaks were unlikely to occur in the same locales in consecutive years. Mortality also appears to be highest in trees in poor condition before defoliation. "Suppressed" trees which are not defoliated can also benefit from defoliation of the overstory which normally shades them out. Suppressed trees may show increasing growth and survival in response to the increased light and the nutrients from moth frass (Leonard 1974). Attempts to determine the moths' long-term effects on forest composition in the United States have, however, been frustrated by lack of data. But there is no doubt that the insect is generally considered to be a serious pest and a nuisance.

Thirty-eight species of birds and numerous small mammals were reported as feeding on the gypsy moth in the United States. In addition, numerous species of parasitoids have been imported as counterpests, but have not succeeded in control. Pathogens of the moth seem to be most effective in increasing mortality, especially viral and bacterial agents. The moth remains out of balance with its environment nevertheless. Swain (1981) suggests that the continuing problem is not due to the fact that the moth is too well established, but that it is not well established enough. He believes that the moth will eventually become integrated into its new ecological home, and when its presence becomes normal, so will its numbers. "Constant pressure from predators, parasites, and disease offers the best chance to control the number of gypsy moths. This will mean continuing to scour Europe and Asia for pests of the gypsy moth. It will mean refraining from poisoning the gypsy-moth pests we already have with the indiscriminate use of insecticides. It may also mean leaving the grass long, the leaves unraked, and the skunk nesting under the back steps."

Mammals

Although problem introductions of microorganisms and insects have usually occurred by mistake, importation and release of vertebrate species have almost always been deliberate (Elton 1958). Accidental introductions of vertebrates have mainly included only rats and mice, some lizards and snakes, and some fishes.

Mammalian introductions were made primarily to provide sources of food and fur or for sport hunting. Occasionally, pest control was the motivation. De Vos et al. (1956) reviewed the worldwide status of introduced mammals and stated that the majority of the introductions had "failed." By this they apparently meant that either the exotics did not become established, or that the failure entailed not fulfilling the purpose of the introduction. These are really two very different outcomes. Although some of the more spectacular ecological disruptions on record have clearly been caused by introduced mammals (e.g., destruction of Australian vegetation by the European rabbit), in many other cases, a clear-cut assessment of damage has not been possible or is a matter of interpretation. Two examples will illustrate.

Reindeer were introduced from Lapland into western Alaska in the late 19th and early 20th centuries to provide a new resource for the Eskimos (Elton 1958). In comparable tundra habitat in Lapland, these grazing herbivores apparently had little or no negative ecological impact due to their migratory habits. In Alaska, the native caribou were also migratory. The introduced reindeer, on the other hand, were not. The animals multiplied tremendously and were allowed to completely graze off the cover of foliose lichens which provided their winter food supply in coastal areas. In 10 years, the population crashed from 650,000 to 25,000 animals. Because lichens grow very slowly, regeneration of the range would require 50 to 300 years (Darling 1956). It would seem, therefore, that the introduction of this animal resulted in an ecological disaster. Darling (1956) pointed out, however, that removal of the smothering blanket of lichens has allowed the arctic shrubs, herbs, sedges, and grasses to see the sun. The tundra bloomed and the decline in caribou and reindeer number was followed by an increase in the number and range of the moose. There is no doubt that an ecological modification occurred, but whether this modification was really highly detrimental may depend on one's point of view.

Another often cited case of disruption involves the mongoose, Herpestes auropunctatus. This animal was introduced into Jamaica from Calcutta in 1872 for control of rats in the sugar cane fields. (The rats were also an introduced species.) The mongoose is an aggressive predator, with very omnivorous food habits and generalized habitat requirements. It is also highly fecund and can produce two litters of two to four pups over a long breeding season each year. From initial introductions of small numbers, the animal spread over the entire island of Jamaica in about 10 years, becoming established as a permanent resident. While it did, in fact, initially prey heavily on rats, the animal soon varied its diet by turning to poultry, ground-nesting birds, water fowl, lizards, snakes, turtle eggs, and land crabs. By the end of its second decade in Jamaica, the mongoose had come to be considered "the greatest pest ever introduced into the island" (Laycock 1966). Unfortunately, its initial success as a rat control agent had already resulted in its additional introduction into Puerto Rico and Hawaii. In both the Caribbean and Hawaii, the mongoose has been blamed for depredations of the native biota so severe as to result in local, if not widespread, extinctions, particularly of ground-nesting birds and reptiles. Field studies by Baldwin et al. (1952) indicated, however, that the effects of predation by man and changes in land-use practices may have had a far greater influence in reducing populations of native species in Hawaii than has predation by the mongoose. They reported that the birds most severely affected by the mongoose are exotic game species and domestic poultry. Several of the native Hawaiian species believed to have been adversely affected have managed to persist and breed on mongoose-inhabited islands. There is evidence from both Jamaica and Hawaii that a new balance has been established and that the mongoose has been incorporated into a new, albeit different, ecological system. It is still regarded as a nuisance, and Hawaiian law makes it illegal to "transport, house, or rendor succor to this pest" (Paine and Zaret 1975). It is worth mentioning that De Vos et al. (1956) commented, "The introduction of a mammal for the sole purpose of controlling pests is almost certainly doomed to failure. Food habits are rarely so specialized that a mammal will feed entirely on the pest to be controlled." On the other hand, planning to control rats by introducing the mongoose was so poorly thought out that apparently no one noted that this predator is diurnal while the rat is nocturnal. Such a level of ignorance of basic facts has been characteristic of many deliberate species introductions in the past.

Birds

No other taxonomic group has been as subject to transport and release in new environments for purely sentimental reasons as have birds. In the 19th century, the importation of foreign birds became a craze both in the United States and abroad. Organized groups known as "acclimatization societies" imported, cared for, and released thousands of birds in the hopes that foreign "songsters" would provide pleasant visual and auditory additions to the native fauna. For the most part, these efforts failed. Their outstanding successes came, however, with the house sparrow and the European starling.

The story of Eugene Scheifflin, the leading force in the American Acclimatization Society, and his desire to introduce all the birds that Shakespeare had mentioned is oft told (Laycock 1966). Suffice it to say that in the case of both the house sparrow and the starling, their habits as destructive agricultural pests were already known long before their introduction into this country. Both birds have become well established specialists in urban and cultivated environments. In this, they are characteristic of the small group of exotic bird species to have become resident in the continental United States. Most, like the skylark and the nightingale, died out after a short time or never got a foothold on survival at all (Elton 1958). This is probably just as well. Sparrows have reportedly displaced native species such as martins, swallows, and wrens. Starlings compete with bluebirds and woodpeckers for nesting sites and have caused millions of dollars of agricultural crop damage and jet aircraft accidents. Attempts to control both species have been unsuccessful and damaging to nontarget wildlife (Courtenay 1978).

Compared to the mere seven or eight exotic bird species that have become permanent members of the continental fauna, the number of successful establishments in Hawaii (46) is very large. This fact reflects the depauperate nature of the native Hawaiian fauna which evolved in extreme isolation (Zimmerman 1963) and the ease with which remote island ecosystems are unbalanced by invading organisms, including man. The limited colonization and radiation of native bird species presumably left large gaps or "unfilled niches," resources available with no species to use them until the arrival of introduced exotics. The extent to which introduced birds helped cause dramatic extinctions by competition with the endemic fauna is not clear. Berger (1972) thinks that one of the more plausible reasons for the extinction of native bird species is that the exotics brought in foreign diseases to which the "natives" had little or no immunity. Destruction of the island vegetation by introduced goats, rabbits, and cattle, or for crop production, has also contributed greatly, and predation by introduced rats and mongoose has certainly helped reduce numbers if not produced extinctions by itself. In any case, the combination of all these aspects of human disruption apparently means that only about a third of the native bird fauna has much chance of survival (Berger 1972).

GENERALIZATIONS ON SPECIES INTRODUCTIONS

No one really knows how many species have spread from their native environments, but Elton (1958) thinks it must be tens of thousands. Of these, the number of organisms that have become established is probably only a fraction (which can still amount to thousands of species), and the number that cause ecological disruptions is a still smaller fraction. Many introduced species only do well in simplified, man-made environments. Although this may mean that the disruption of natural ecosystems is often minimal, the impact that exotics can have on human life (e.g., agricultural pests) is usually therefore more intense. Thus, although the percentage of introduced species causing dislocation in the native biota may be small, this may not be the most important aspect of the problem. At any rate, ecologists do not really know what the numbers are, particularly if microorganisms are included, and meaningful quantitative generalizations are therefore impossible to make. The consensus amongst ecologists is that the outcome of a species introduction is not predictable (Bates 1956, Laycock 1966, Paine and Faret 1975, Courtenay 1978). Rather, the introduction of exotics is viewed as a game of chance with the possibility of both high risks and rewards.

What can definitely be said about exotic introductions is that the outcome is determined by both the nature of the invaded environment and the nature of the invading organism. Environments that are particularly vulnerable are those that are isolated, simplified, and/or stressed and disturbed. The limited floras and faunas of remote islands have usually undergone drastic and often permanent modifications when invaded by continental colonizers. Agricultural and other human-created systems provide ready targets for the proliferation of imported insect pests and weeds, and even mature ecosystems that are subject to perturbation and stress may be unable to check invaders when normal homeostatic mechanisms are disrupted.

As for what makes a successful exotic, the most important requirements would seem to be that it not be overly specialized, that it have high reproductive and dispersal capabilities, and that it be a good or aggressive competitor. All of these factors are generally related to an ability to be opportunistic and take advantage of whatever resources are available. It also helps that many exotics make their appearance unaccompanied by their own predators and parasites and frequently enter enviroments with no defenses tailored to the particular characteristics of the invader.

The changes brought about by an introduction can vary from nearly unnoticeable to dramatic and unmistakable. Competition between exotics and natives can result in the reduction or exclusion of native forms, as can predation, parasitism, or pathogenicity on the part of the invader. The stress placed on a system by a foreign species may also contribute to the establishment of other exotics to cause further unbalance. Over the long term, however, a new organism may finally become integrated into the system it has penetrated. This integration is usually marked by a major reduction in number of individuals The reasons for the decline of exotics, when this occurs, are just as obscure as the reasons for their explosive spread in the first place (Elton 1958). Two things must, however, be kept in mind. The more disturbed, artificial, or simplified an environment is, the less likely it is that a new balance can be struck in a reasonable time. Second, even if an exotic becomes integrated and is no longer explosive, the system it entered has been modified and is different and perhaps simpler. The desirability of creating such new systems will, in many cases, remain a matter of debate.

CREATION OF RESISTANT GENOTYPES

Biological resistance to chemicals may be defined as a decreased response on the part of an organism to a control agent as a result of application of that control agent. Development of resistance is a dynamic adaptive reaction to intense, though unintentional, selection by man. Usually, resistant genotypes make up part of a population's innate genetic diversity, but exist only at very low frequencies until acted upon by selection. In bacteria, however, mechanisms do exist for transmitting resistance between species and even genera, so that genetically determined resistance might be acquired across taxonomic boundaries by species without the necessary raw material of their own. In any case, the result of selection with a control agent is a proliferation of gene combinations which were probably exceedingly rare before exposure. In this sense, evolution of organisms with resistant genotypes is a reasonable analogy for production of new genotypes by genetic engineering. The following discussion examines some of the mechanisms and implications of antibiotic resistance in bacteria and pesticide resistance in insects.

Antibiotic Resistance

A discussion of antibiotic resistance in bacteria is particularly appropriate not only because it represents natural proliferation of novel genotypes but also because it involves plasmids, the molecular entities which are typically the vectors of genetic engineering.

When antibiotics were first introduced, they were extremely effective in killing bacteria (Broda 1979). Initially sensitive bacterial strains have, however, rapidly and repeatedly become resistant to each new antibiotic that is introduced. The clinical significance of the phenomenon is great in that many problems in the treatment of pathogen-caused illness have arisen with serious consequences. For example, in 1969-70, a major epidemic of bacillary dysentery occurred in Mexico and Central America (Elwell and Shipley 1980). Over 500,000 clinical cases were reported and fatality rates were as high as 35%. The organism responsible, Shigella dysenteriae(1), was shown to be resistant to chloramphenicol, tetracycline, streptomycin, and sulfadiazine, all drugs commonly used to treat dysentery.

Other bacteria are known to be naturally resistant to most commonly used antibiotics and can therefore only be controlled by a very limited number of chemicals. Pseudomonas aeruginosa is one such organism that commonly grows in hospital environments and can cause local infections, particularly on burns. It is a principal cause of death by respiratory tract infection in children suffering from cystic fibrosis (Broda 1979) and is controllable only with carbenicillin and gentamicin. In a hospital burn unit in Birmingham in 1969, P. aeruginosa strains resistant to carbenicillin appeared and in two to three months had replaced all other strains in the wards (Broda 1979). The use of carbenicillin had to be discontinued, leaving only one effective drug in the medical arsenal.

The very widespread appearance of organisms resistant to antibiotics is believed to be partly due to gross overuse of antibiotics. In many countries in which multiple resistant forms of dysentery and typhoid bacilli have arisen, the sale of antibiotics is unrestricted and requires no prescription. This situation has presumably allowed intense selection for resistant forms by flooding the human environment with an abundance of control agents. In the United States, antibiotic use in livestock production is widespread. Broda (1979) reports that _E. coli_ found in calves, pigs, and poultry are now usually resistant to sulphonamides and many are also resistant to ampicillin, streptomycin, and tetracycline. Beef, veal, pork, and chicken are often contaminated with _E. coli_, and ingestion of live bacteria in meats is a possible route of transfer to man. Although _E. coli_ is a normal gut commensal in humans, resistant forms which inhabit humans pose a problem because of their potential to transmit their resistance to other bacteria, including pathogens. The mechanism of this transmission involves plasmids, which are the primary vector for transfer of new genes into bacteria in the recombinant DNA technique.

Plasmids are autonomously replicating extranuclear (extrachromosomal) genetic elements. Like the material of the bacterial chromosome, the DNA of plasmids encodes genetic information. The kinds of information frequently encountered on plasmids are fairly diverse, but the most notable ones are resistance factors for antibiotics and heavy metals (R plasmids), and genes that specify functions which allow plasmids to transfer from cell to cell (F factors or conjugative plasmids) (Davies and Smith 1978, Broda 1979). There are also plasmids known to encode production of antibiotics (Hopwood 1978) and others which specify properties that cause pathogenicity, the so-called "virulence" plasmids (Elwell and Shipley 1980). Plasmids are frequently referred to as "dispensable" elements (e.g., Elwell and Shipley 1980) and are thought to govern functions which are nonessential for normal growth and metabolism of the bacterial host. The genes they carry are often for supplementary activities which allow the host's survival in adverse envirnments. There is, however, a great deal of DNA in plasmids which is of unknown function (Davies and Smith 1978).

Davies and Smith reviewed the role of plasmids in determining antibiotic resistance. They distinguish seven theoretical biochemical mechanisms of resistance of which only four are empirically known to exist. Of these four, two are likely to be nearly entirely due to plasmids, while the remaining two may be either chromosomally or plasmid determined. They point out, however, that "whether or not resistance is plasmid or chromosomally determined is academic, since most resistance characters are likely to be transposable." "Transposable" genetic elements are discrete segments of DNA that are apparently common constituents of plasmid, virus, and bacterial chromosome. They exhibit the unusual property of mobility, moving encoded traits between chromosomal and other locations. The encoded traits are frequently identified as conferring antibiotic resistance or the ability to produce toxins (Kopecko 1980). This means that even if DNA that confers resistance is sometimes part of the bacterial chromosome, it may be capable of movement back and forth between chromosome and plasmid. For instance, the tetracycline resistance gene occurs on a "transposon" that has been found on resistance plasmids. The genes for β-lactam (penicillin) resistance are also commonly found on transposable elements. Many extrachromosal elements also encode their own endonucleases which are enzymes also used to make recombinant DNA; they thus appear to be capable of "natural genetic engineering" (Reanney 1976). Most, if not all, mechanisms of antibiotic resistance may therefore be likely to be plasmid-borne eventually.

The significance of this possibility is great because of the ubiquitous nature of plasmids and the ease with which they are transferred between bacteria. Conjugative (transmissable) plasmids have only been identified for gram-negative bacteria. Gram-positive bacteria do, however, have nonconjugative plasmids with many of the same resistance characters and these can be expressed in gram-negative species when artificially transferred (Davies and Smith 1978). Even given this limitation, Reanney (1976) believes that the potential for exchange of plasmids (and phages) between different species and genera is so large that, at least in bacteria, the species concept may no longer be meaningful. No single organism can evolve in genetic isolation from other organisms with which it shares a common environment. "The general principle that emerges is that in any ecosystem where the microflora is connected by a sufficiently large number of extrachromosomal elements, the size of the entity upon which selection acts may exceed by perhaps several orders of magnitude the size of the gene pool of a monoclonal population . . ." (Reanney 1976).

Many authors have speculated on how and why plasmids arose. Reanney (1976) suggests that the genes for inactivation of antibiotics first arose in the organisms that produce antibiotics and constitute the ancestral reservoir of such genes. The transfer of these genes by extrachromosal element vehicles may have allowed their spread into many diverse organisms. In effect, the bacteria may have "stolen" them from their "inventor." Although the mechanism for this event is a matter of conjecture, both Reanney (1976) and Davies and Smith (1978) point to the presence of very similar or identical characters in widely divergent taxonomic groups as evidence of possible common origin from an unknown source. Reanney even goes so far as to suggest that transmissible extrachromosal elements, probably viruses, can account for the presence of unusual chemicals in widely divergent and otherwise unrelated plant groups.

The selective advantage of plasmids is also a matter for speculation. Reanney believes that extrachromosomal elements in general provide a mechanism by which a high degree of genetic variation may be maintained among bacteria while allowing them to minimize the metabolic cost of maintaining a large genome. A large chromosomal genome would be a disadvantage to organisms which need to replicate faster than competing organisms to survive. Since up to 20% of the DNA in a bacterium may be in plasmid form, and 30% of coliform DNA may consist of prophage, these elements offer the possibility of genome "sizing." When not needed, the cell could trim down its genetic complement, but when needed, the additional variation offered by plasmids can be seized in response to stress conditions.

Koch (1981) also believes that plasmids allow unusually rapid acquisition of additional functions and without the necessity of disrupting balanced chromosomal genomes by incorporation of new mutations. It is his view that the resistance mechanisms that appear today in response to man's use of antibiotics do not represent de novo evolution at the primary gene level. Rather, "as the result of the new ways and dimensions in which old selective pressures are exerted, the old answers are recalled and reactivated." In closing he remarks, "If humans exploit a natural compound biosynthesized by an organism that had to produce a defense mechanism against its own product, then this mechanism of protection may find its way into the human pathogens. As the penultimate resort, since antibiotics that we will use attack certain procaryotes but not mammals, the procaryotes may respond by adopting the mammalian way. There will always be an Achilles' heel. If nothing else, procaryotes may once again engage in de novo evolution of new resistance mechanisms."

Insecticide Resistance

The subject of resistance to insecticide is included largely to reinforce this single point: small changes in an organism's genetic information can produce large changes in its functioning and in turn have an extremely large impact on its economic status. The subject also contains some interesting lessons on the adaptability and dynamic nature of living things.

In 1976, the number of arthropod species in which resistant strains had evolved reached 364, which represented a 62.5% increase over the number surveyed in 1967 (Georghiou and Taylor 1976). In the same period, there were also significant increases in the geographical distribution of resistant populations and in the spectrum of chemicals involved. Georghiou and Taylor reported that at least 57 commercial pesticides are affected by resistance, including DDT, most cyclodienes, and many organophosphates and carbamates, and that cross-resistance and multiple resistance have greatly depleted the available insecticide resources for a number of key pests. They enumerated the impacts of resistance in terms of ecological disruption, financial loss, and socioeconomic effects.

First, disruptive effects of pesticide use on beneficial insect species are accentuated as dosages and application rates are increased to combat developing resistance. Because beneficial insects are generally present in much lower densities, they rarely also evolve resistant strains. Second, the necessity to increase dosage and application rates results in greatly increased costs to the applicator. In addition, rapid development of resistance and cross-resistance conferred from other compounds may make the useful lifetime of newly developed pesticides very brief. Thus, use of new compounds may not return the high monetary investment involved in their development.

Third, socioeconomic dislocations can be severe. Reynolds (1976) reviews, for example, the history of the impact of resistance development in cotton pests in southern Texas and northeastern Mexico. Cotton is the field crop most severely affected by resistance development. About 47% of the insecticides applied in agriculture in the United States are used on this one crop. Thus, selection pressures on cotton pests have been extreme, and 33 species of cotton pests have developed resistance. A few of these, including the boll weevil (Anthonomus grandis) are resistant throughout most of their range. Serious difficulties in Texas began in the 1950's when first the boll weevil and then the tobacco budworm (Heliothis zea) and boll worm (H. virescens) developed resistance to the organochlorine insecticides. Use of replacement organophosphorus insecticides to control the boll weevil resulted in reduction of beneficial insects, and, in turn, tremendous outbreaks of the Heliothis species occurred in the absence of their natural enemies. Organophosphorus dosages and applications then had to be increased to control tobacco budworm. Many cotton farmers treated their fields 15, 20, or more times but still suffered severe losses. Without boll weevil control, good yields could not be produced, but with weevil control, tobacco budworm jeopardized production. Even farmers who had good yields still had small profit margins due to the high cost of pesticide application. In neighboring areas of Mexico, effects were much worse. Several hundred thousand hectares of cotton went out of production; gins, compresses, and oil mills closed; and farm workers were forced to move. In addition, illnesses of spray applicators and farm workers were frequent due to exposure to the repeated applications of high dosages of toxic organophosphates.

In Nicaragua, cotton growers in the 1960's applied an average of 25 to 30 insecticide treatments per year to combat resistant cotton pests. Thousands of insectide poisonings and hundreds of human deaths were reported, and the highest level of DDT and BHC residues in mother's milk in the world were recorded (Vaughan and Leon Q. 1976). In addition, cases of malaria increased because the heavy applications of pesticides had also promoted resistance in its vector, the mosquito *Anopheles albimanus*. This phenomenon is also believed to have occurred in other countries (Pal 1976).

In terms of its medical impact, the development of pesticide resistance is now thought to be "the biggest single obstacle in the struggle against vector-borne disease" (Pal 1976). Insecticide resistance was reported to affect areas in which one-third of the total population of malarious regions resided in 1976. The necessity to continually change insecticides has resulted in cost increases and ensuing financial hardship in developing countries. Pal stated, "Even if financial constraints could be solved and new effective compounds could be made available, malaria control concept and strategy. . . based on the use of chemicals which will produce resistance sooner or later will not be able to achieve any major impact on communicable diseases."

How and why do insects develop pesticide resistance? Simply put, populations become resistant due to selection of individuals with genes that permit them to survive the exposure and reproduce (Waterhouse 1976). Some pest species apparently have a genetic diversity sufficient to develop multiple resistance mechanisms to each of a succession of pesticides. Each new chemical selects one or more mechanisms of resistance and each mechanism may in turn confer cross resistance to several other insecticides to which the pest has not even been exposed (Georghiou and Taylor 1976). These mechanisms also apparently contribute to retention of resistance to discontinued chemicals. Although several studies have shown that resistant populations have lower fitness, fitness has also been observed to improve with continued selection, presumably by coadaptation of the genome. Background changes in residual inheritance of the resistant genome makes it possible for an insect species to regain resistance as soon as a discontinued insecticide is reapplied (Brown 1976). Danish houseflies, for example, recovered DDT and cyclodiene resistance in two months when it had taken them five years to lose it and two years to develop the first time. According to Waterhouse (1976), no instances have been reported in which field resistance declined enough to enable re-introduction of a pesticide after resistance had developed.

Resistance usually does not involve visible changes in the behavior or morphology of an insect. Rather, resistance is caused by subtle changes in the biochemistry or physiology of the pest or by a change in its membrane permeability (Waterhouse 1976). The most common mechanisms of resistance at the biochemical level involve: (1) alterations of a target enzyme which decrease its sensitivity to a pesticide (e.g., acetylcholinesterase changes in response to organophosphorus or carbamate compounds), (2) decreased absorption or lower absorption rates which allow more time for detoxification, and (3) detoxification. Interestingly, the mode of action of, and therefore the mechanisms of resistance to, the cyclodienes is very poorly understood (Plapp 1976). Cross resistance always extends to all the cyclodienes (heptachlor, chlordane, aldrin, dieldrin, and endrin) regardless of the selecting agent or insect group. Although the mechanisms of resistance are diverse, they have time and time again turned out to be due to monofactorial (single gene) inheritance (Brown 1977). In the case of DDT-resistance, at least three different mechanisms are known--dehydrochlorination, oxidation, and reduced nerve sensitivity. Each mechanism is controlled by a single gene, and in concert the three produce resistance intensities that are muliplicative rather than additive (Brown 1976).

Conclusions

The use of an ecological approach is judged to be valid for assessing the environmental risks associated with recombinant organisms. Microorganisms are likely to be of most immediate importance in applied genetics. Microbial ecosystems exhibit the same ecological properties and processes as systems of higher organisms. The likelihood of an organism becoming established and persisting in a given environment is an ecological question regardless of the origin or nature of the differences that make such an organism "exotic" or "novel." The proportion of the genome which is "new" is not necessarily correlated with the degree of impact an organism can have on an ecological system. In fact, an introduced organism which is very similar to those with which it must compete may be more likely to survive than an organism which is moderately or very different. In this case "similar" is meant to imply that the range of environmental properties (e.g., temperature, moisture level, habitat type, etc.) tolerated by one organism overlaps the range tolerated by another. Looking at it in another way, one would not expect a soil bacterium to have requirements very close to those of an aquatic bacterium.

Unfortunately, no quantitative assessment of the risk of ecological damage by recombinant organisms can really be made on the basis of existing ecological knowledge. Efforts directed at devising a numerical probability for establishment and disruption based on the number of negative results that have already occurred would not be meaningful or fruitful for a number of reasons. First, what constitutes a negative result is not always clear and may be a matter of interpretation. Second, very little attention is ever paid to exotic organisms unless they become a problem, but we do not really have any idea how many have been introduced and failed to get a foothold. Third, ecologists do not understand enough about the complex interactions in an ecosystem to be able to predict the outcome of an introduction. There are too many uncontrolled and unknown factors at this point to handle new situations on anything other than a case-by-case basis. If we are to have meaningful probabilities, they will have to be generated by experimental research with model ecosystems. Fortunately, microorganisms readily lend themselves to laboratory experimentation, and research of this type seems to be the most appropriate method of characterizing risk with some hope of valid, generalizable results.

Summary

One category of objection to the release of organisms produced by genetic engineering is based on the fear that such organisms may persist in the environment and damage existing ecosystems. An assessment of environmental risk thus involves an ecological question analogous to the introduction of exotic species which has been known to produce serious ecological disruptions. An investigation of the literature on exotic introductions reveals, however, that foreign species do not invariably produce adverse changes. Ecologists believe that only a fraction of immigrating species actually produces ecological dislocation while the majority probably fail to penetrate existing biotic assemblages. Stressed or simplified environments are, however, more vulnerable to successful invasion. Unfortunately, because very little information has ever been collected to document the number or causes of failed introductions, it is impossible to quantify the probability that any introduced species will or will not cause serious disturbance purely on the basis of historical evidence.

The development and spread of genotypes that confer resistance to chemical control agents in insects and microorganisms is also analogous to genetic engineering in that human activity contributes to the spread of new genotypes. In both groups of organisms, resistant genotypes can come to predominate in even geographically widespread populations with great rapidity. Resistance to pesticides in insects is usually found to be determined by single genes. In bacteria, antibiotic resistance genes are usually, if not always, associated with the extrachromosomal genetic elements known as plasmids. Bacteria seem to be able to

transmit plasmid-borne genes between species and genera with facility. The ease with which new genes can be inserted into bacteria via plasmid vectors in recombinant technology is thus a two-edged sword. It may be very difficult to keep inserted genes isolated in single bacterial strains.

The evaluation of the literature on which this report is based suggests that an ecological approach for risk assessment is appropriate. Microorganisms, for which genetic engineering is of most immediate importance, exhibit the same ecological properties as higher organisms. The proportion of an organism's genome which is novel has no direct correlation with the magnitude of impact such a change may have in economic, medical, or ecological terms. Meaningful probabilities for persistance of engineered organisms in the environment will have to be generated by experiment, probably with model microbial ecosystems.

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APPENDIX B

New York State College of Agriculture and Life Sciences
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Cornell University
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August 5, 1983

The Honorable Albert Gore, Jr.
U. S. House of Representatives
Committee on Science and Technology
Suite 2321 Rayburn House Office Building
Washington, DC 20515

Dear Mr. Gore:

This letter is in response to your request of July 25 that I provide answers to the series of questions. It is a pleasure to respond to that request.

1. Is the deliberate or accidental release of new microorganisms into the environment likely to present more difficult problems than the introduction of other kinds of organisms?

   Most newly created microorganisms will likely not survive. Hence, as a rule, the accidental release of such organisms will pose no practical problems. However, deliberately released microorganisms will have ecologically beneficial traits in order that they can become established in natural environments, although in this instance the purpose would be to bring about some beneficial effect. However, the fact that they do have survival and growth capabilities in natural environments indicates that they are different from the many organisms that do not survive in nature. Moreover, a number of newly created organisms that are accidentially released will also survive, and some of these will also grow in natural environments. Hence, even these organisms will pose more difficult problems than organisms that already exist.

   As pointed out in the hearings by Dr. Hardy, microorganisms pose special problems in contrast with other species. They are difficult to contain, and they are highly mobile. Moreover, their capacity to multiply is enormous. Therefore, a newly introduced microorganism, as contrasted with a newly introduced plant or animal, may have the capacity to move rapidly from the site of introduction, multiply rapidly and possibly have deleterious effects. As Dr. Hardy also pointed out, it is easier to control larger organisms with selective chemicals than to control introduced microorganisms.

2. What lessons are to be learned from our past experiences with the introduction of other kinds of organisms?

   Our experience with existing organisms indicates that most do not survive in nature. Of those that do survive in habitats in which they were initially alien, few will grow, and few will have a significant ecological effect. Nevertheless, some newly introduced organisms have survived, have grown and have had an effect. Furthermore, existing information is not adequate to predict, based upon a priori knowledge of the organisms and without testing, whether a newly introduced organism will survive, grow or have an effect. It is for this reason that we maintain quarantines (i.e., the paucity of knowledge of how to predict their effects).

3. The risks of new genotypes are hard to quantify or identify. How should we proceed given this uncertainty?

   Because it is likely that genetically engineered microorganisms will have benefits in industry and agriculture, we should not approach the uncertainty by prohibiting all of the potential uses. On the other hand, I believe that, as with chemicals whose effects are initially unknown, a reasonable regulatory approach can be established. This approach would require that the probabilities of survival, growth, reaching a colonizable environment, and causing a detrimental effect be established before there is release or before there is experimentation in open environments. The regulatory approach should be designed to encourage the practical uses of these genetically engineered microorganisms while minimizing their detrimental effects. Assessments of survival and growth can probably be done at low cost and with existing technologies, or technologies that can be developed in the very near future, but defining meaningful regulations will require research to develop means to assess effects on animals, plants and ecosystems at low cost and in a reasonably short period of time.

4. How do we construct a model for evaluating the risks and benefits presented by the introduction of new genetically engineered organisms into the environment?

   Such a model should not be appreciably different from the models that are currently used for evaluating the risks and benefits of new chemicals. The chief difference is the need to establish the components of risk and to devise an appropriate means of assessing the risks with individual organisms that are either proposed for introduction into natural environments or that may be inadvertently released into those environments.

5. How should we test new organisms to ensure that they are environmentally safe before they are released?

   Such tests can be conducted by establishing an appropriate regulatory procedure, such as that described briefly above, and requiring industry to provide appropriate information to the regulatory agency and allowing sufficient time for the regulatory agency to evaluate the information that is provided to them.

6. Would some sort of environmental impact statement for genetic engineering be a good idea?

   Possibly yes. The chief concern I have in this regard is the expense. However, if an organism is likely to grow and is likely to have an effect, then I believe it is essential that the regulatory agency require an impact statement. However, if the organism is unlikely to survive, to grow, to contact a suitable host or other environment in which it can bring about an effect and to bring about that detrimental effect, I see no need for the company or other group disseminating that organism to take the time or expend the funds to prepare such a statement.

   On the other hand, a general environmental impact statement for genetic engineering of a variety of sorts would be appropriate. This would not be organism-specific but might be specific for categories of microorganisms, different environments and categories of uses.

7. How soon do you see widespread releases of new organisms becoming a reality?

   Almost immediately. Several research groups are endeavoring to develop such organisms, and there are indications that some of these developments are close to fruition. If this is the case and the approach is feasible, I expect that the organisms would be disseminated quite soon.

8. What is your opinion of the recent approval given by the NIH RAC to three field tests of genetically engineered plants?

   My knowledge of these tests is very skimpy, and I do not have the background information that was provided to the RAC. Hence, it would be inappropriate for me to venture an opinion.

9. What should be the role of the federal government in overseeing this technology?

   Many large companies have a good record in minimizing environmental hazards. However, there are several notorious examples of large companies that have contributed to environmental deterioration. The same is undoubtedly true with regard to genetic engineering technology. Furthermore, small companies with little capital can also develop genetically engineered microorganisms, and I believe that many of these companies would not have the scruples that much of the heavy chemical industry has. Furthermore, they would not have the trained personnel to perform many of the needed tests. In addition, university researchers are active in this field, and they do not have the pressure of regulation and the competence in areas of environmental assessments (in university programs concerned with genetic engineering) so that they may inadvertently conduct dangerous types of experiments relative to environmental concerns. Hence, I believe it is essential that the federal government be directly involved in the regulation of the technology. The appropriate agency would be one that has competency not only in genetic engineering but also in environmental matters.

10. Do you feel that the federal agencies currently have the technical capabilities and resouces to reach reasonable decisions and adequately consider benefits and risks?

    No individual agency at the present time does. NIH has the technical capabilities and resources to evaluate issues that relate to consequences to human health, but it does not have the technical skills or resources appropriate for environmental issues. EPA has the technical skills for evaluating environmental stresses but does not have adequate personnel competent in genetic engineering. Neither of these agencies presently has the resources to do meaningful tests in this field, moreover.

11. Where, if anywhere, do gaps exist in our regulatory structure for approving and controlling releases of genetically modified organisms into our environment?

    As pointed out in my answer to the preceeding question, individual agencies have some of the skills, but no single agency has all of the skills needed for approving and controlling releases of genetically modified organisms into our environment. Hence, either two agencies should together be involved in the regulation or one agency should be given the responsibility. The latter seems to be the more practical approach. In addition, one agency, presumably the one that has the regulatory authority, should develop and in-house capability for doing the needed research in support of the regulatory needs and also should receive funding for supporting extramural research in this area.

12. What are our options with respect to regulating the introduction of these organisms into the environment?

    One option is to do nothing. Associated with this option is the likelihood, admittedly with low probability, that there will be major undesirable changes that affect plants, animals, humans or the functioning of natural ecosystems. A second option is to assign the responsibility to NIH RAC. This option is undesirable because NIH does not have the regulatory authority or the needed competence, and the committee does not have the personnel to assess problems relating to natural environments. A third option is to assign regulatory authority to EPA under TOSCA. As pointed out by OTA at the hearings, this agency may presently have the statutory authority to regulate, but there is some question in this regard. Moreover, the existing framework of TOSCA is not sufficiently strong to handle problems that deal with a microorganism (as a toxic substance) that has the capacity to expand the base of its hazard. TOSCA is designed for substances that are not communicable, and communicable agents pose unique problems which chemicals do not.

13. Do we need new legislation?

    I believe that the most effective way of regulating genetically engineered organisms is to enact legislation that is specifically designed for this purpose. This legislation should enable the agency given the regulatory authority to acquire personnel, develop an appropriate regulatory approach, and perform the needed environmental evaluations and research in order to protect the public and our environment.

Sincerely yours,

M. Alexand

M. Alexander, Professor
Soil Microbiology

dm

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August 15, 1983

The Honorable Albert Gore
Chairman
Subcommittee on Investigations and Oversight
Committee on Science and Technology
U.S. House of Representatives
Suite 2321 Rayburn House Office Building
Washington, D.C. 20515

Dear Mr. Gore,

Enclosed are my answers to the additional questions from the June 22 hearing. I am sorry to have been so long in responding, but I've been out of town for much of the past two weeks. If there are any further questions, please feel free to contact me at any time.

Sincerely,

Fran Sharples

Frances E. Sharples

FES:sml

Is the deliberate or accidental release of new microorganisms into the environment likely to present more difficult problems than the introduction of other kinds of organisms?

Only in one sense that I can think of. The fact that genetic engineering is mostly accomplished using plasmids may mean that "new" genes introduced into an ecological community via an engineered organism could be transmissable to native organisms. Bacteria are known to be able to exchange plasmids between different species and even genera though whether the phenomenon occurs extensively outside the laboratory is not known. Thus the introduction of an engineered organism into the environment may have not only the potential to cause the kind of ecological disruption that has been associated with some "exotic" species, but also may have the potential to pass on "novel" genes into wild organisms. For this reason, until our understanding of plasmids is improved and an ability to isolate them permanently in engineered bacteria is confirmed, we would probably not want to allow the release of organisms bearing genes which might produce undesirable effects if spread to other wild bacteria, eg. antibiotic resistance genes or genes associated with pathogenicity.

What lessons are to be learned from our past experiences with the introduction of other kinds of organisms?

To answer this question, I would like to summarize the conclusions already presented in my testimony and add a few more points.

- I believe that the analogy between exotic species introductions and introduction of organisms with man-made gene combinations is a valid one. The proportion of an organism's genome which is novel is not directly correlated with the magnitude of impact that a genetic change may have in economic, medical, or ecological terms.

- Unfortunately, the outcome of an introduction is not currently predictable and the risk of a disruption is not currently quantifiable. We do, however, know that only a small fraction of introductions result in ecological dislocations. Thus, the most reasonable inference that can be drawn is that the risks associated with introduction of novel organisms are probably low but are definitely not zero.

- Disturbed, isolated, or simplified environments are more vulnerable to penetration by and successful establishment of an invading foreign species. Thus, polluted and agricultural environments are more likely to be locations of successful establishment.

- Successful invaders are often adaptable and opportunistic organisms with flexible nutritional requirements, high reproductive rates, and good dispersal capability. Thus, an organism with narrow tolerance ranges is, in general, less likely to survive when introduced into a new environment unless it is "preadapted" for it. (See last point on this question).

- Introductions can have both highly positive and highly negative effects. Eventually an exotic organism may become integrated into an ecosystem it has penetrated and cease to become a noticeable problem. The ecosystem is, however, different, perhaps less complex, and perhaps more vulnerable afterward.

- Ignorance of basic biological facts has been common in attempts to introduce exotic species in the past. For example, the mongoose, considered a destructive pest on Caribbean islands and in Hawaii, was introduced in these locations to control rats (also introduced). The plan for rat control neglected to allow for the fact that rats are nocturual while the mongoose is active in daylight hours. Similarly, both starlings and house sparrows were known to be agricultural pests before their introduction to North America. Careful attention to biological facts should help to avoid at least the more obvious sorts of mistakes with genetically engineered organisms.

- An introduced organism can be "pre-adapted" for success in a particular kind of environment. That is, if the characteristics of the environment into which an organism is to be introduced match those of the environment in which the organism evolved in the first place, the introduction is more likely to succeed. For example, introduced annual grasses from the Mediterranean parts of Europe are believed to have almost completely displaced the native perennial bunch grasses of California. The European annuals were adapted to the Mediterranean type of climate (long, dry summers and mild, wet winters) which is also characteristic of California, and had also evolved an ability to tolerate grazing pressure and compete aggressively with perennial grasses. Thus, when introduced to California, the annual grasses of Mediterranean Europe were entering an environment in which they were predisposed to succeed. The parallel situation for genetically engineered organisms might be to engineer the desired genes into bacteria which occur naturally in whatever environment will be the location of a release. This would help to ensure that the modified organism would have some measure of success in persisting long enough to do its job. The only problem is, of course, that only a few organisms are currently well understood in genetic terms, and it may not always be possible to use a naturally-occurring inhabitant for the laboratory manipulations that are required.

In most of the proposed applications of genetically engineered microorganisms for industrial or agricultural purposes, the benefits are reasonable easy to identify. The risks, on the other hand, are much harder to quantity, or even identify. How shoud we proceed given this uncertainty?

If it is assumed that no immediate changes in Federal regulatory structure are forthcoming, it seems to me that the Recombinant DNA Advisory Committee and the EPA could start doing a couple of things.

First, the EPA could start supporting research on designing test procedures for determining the fate of engineered organisms and the safety of releasing them. They will probably want to look at microcosm designs. They will need to do some serious consulting with ecologists and geneticists to evaluate research approaches and results. EPA can take care of potential commercial applications, but if it intends to regulate under TSCA, they will not have control over field testing in the context of research and development. The RAC will have to handle that.

The RAC is now trying to "staff up" with individuals who represent the ecological discipline. Once this has been accomplished, I think the RAC might try to set down some subsidiary guidelines to facilitate consideration of requests for waiver of the prohibition on release for field testing purposes. These subsidiary guidelines could be similar to the original NIH guidelines in categorizing classes of tests which may or may not be allowed given current knowledge. For example, the RAC might continue to have a class of strictly prohibited experiments which cover organisms which contain DNA from pathogens, which make toxins, or which contain antibiotic resistance genes. Another class of experiments might be ones that are conditionally permissable, and the conditions could encompass a variety of aspects. For example, the RAC might require that a scientist requesting permission to field test an organism in this class be able to first demonstrate reasonably reliable knowledge of what genes have been engineered into an orgnism and that some weakness or self-destruct mechanism has also been incorporated to help ensure that the organism con be readily destroyed when it has performed its fuction. When I say, "reliable knowledge of what genes have been engineered into an organism", I mean the following. Some waste-degrading organisms are being developed by mixing large amounts of uncharacterized genetic information together, and then selecting out clones which can degrade a target chemical. For example, Dr. Chakrabarty's 2,4,5-T degrading bacteria were developed, as I understand it, by mixing laboratory strains with bacteria which naturally occur in landfills but are not well characterized genetically. I don't believe that Dr. Chakrabarty knows exactly from what organism the 2,4,5-T degrading capability was derived, and what other capabilities came along with it. Dr. Lindow, on the other hand, seems to have a better understanding of what genes he is dealing with because he has constructed total genome libraries from the few selected species of bacteria he is working with.

At any rate, some subsidiary guidelines could enable the RAC to retain control in that all requests for permission to field test would still have to be approved on a case-by-case basis, but the consideration process might be greatly speeded up. Investigators would also know more about what is expected to get approval and could pursue fulfilling requirements rather than be stalled by major uncertainties.

How do we construct a model for evaluating the risks and benefits presented by the introduction of new genetically engineered organisms into the environment? How should we test new organisms to ensure that they are environmentally safe before they are released?

The consensus among ecologists at this point is that microcosms would be the most appropriate starting point. I recently met a researcher at the University of Washington in Seattle (Dr. Frieda Taub) who believes that a microcosm she has developed for testing chemical toxicity might also be suitable for testing the behavior of recombinant organisms. Dr. Taub's system is a freshwater aquatic one and is "gnotobiotic," i.e., an artificial ecosystem composed of known organisms selected by her. This fact means that the results of any tests performed with the system should be reproducible no matter who performs the tests as long as the same starting materials are used. This would not be the case with microcosms derived by sampling natural communities, since no two naturally-derived microcosms are likely to be exactly alike. Whether Dr. Taub's system will actually lend itself to testing of organisms rather than chemicals remains to be determined. Even if it did, comparable systems would still also have to be developed for soil environments, marine environments, etc. And it would still require a leap of faith to believe that the behavior of an organism in such an artificial ecosystem gives an accurate picture of what it might do in a natural environment. Dr. Taub's system does, at least, behave like natural systems, and this is an indication of some promise. There is, it goes without saying, a great deal more work to be done before the ecological community feels it has valid tools to work with.

Would some sort of environmental impact statement for genetic engineering be a good idea?

Although I am a firm believer in the value of impact statements (I made a living writing them for four years), I am not convinced that an EIS would help much at this point. There is not enough concrete information available for anything other than an extremely generic treatment, in which case it is not clear how an EIS would represent an improvement over the documents that already exist (e.g., the assessments done by OTA). Perhaps once the issues, risks, and proposed federal actions are clarified, an EIS would be appropriate later.

How soon do you see widespread releases of new organisms becoming a reality?

The impressions I have formed of what industry is up to are as follows. There is a great deal of confusion about what is and is not-permitted under existing regulations, and there is also a great fear of liability in the event of an environmental disruption. Consequently, most of the industrial entities in a position to develop and use recombinant organisms in an environmental release context are holding and doing very little. It would seem that confusion and apprehension is putting a considerable damper on the rate at which research for quite beneficial purposes is conducted. On the other hand, a few companies are planning on going to the RAC or have already gone to the RAC to get permission to field test their organisms. This is likely to become more and more frequent in the future. I would guess that over the next one to two years, there will have to be some serious decisions made at the Federal level on how to handle the question of environmental release. If there are no decisions and no structure is set up to accomodate or allow field testing, I think we will begin to see commercial firms eventually bypassing the RAC and pursuing product development without benefit of Federal oversight. On the other hand, if a smoothly operating approval system could be constructed, I think we might see product marketing in the next two to five years.

What is your opinion of the recent approval given by the NIH RAC to three field tests of genetically engineered organisms?

I think the RAC's decisions on these three particular cases were probably the correct ones. Although I am not familiar with the details of the two plant cases, I am reasonably sure that modified corn, tomato and tobacco plants probably do not present much of a threat to the general health and safety of the nation. Most domesticated crop plants are almost totally dependent on the care they receive from humans and cannot compete in the wild. In the case of Dr. Lindow's bacteria, I believe he is probably correct in asserting that they do not pose significant risks to health or the environment. The modified organisms are derived from populations that occur naturally in the habitat into which the release will be made, and the modifications do, in fact, appear to be very minor ones. He also seems to have a good understanding of exactly what he is dealing with genetically, which is, I believe, an important aspect of the case.

What should be the role of the Federal government in overseeing this technology?

I believe the Federal role is to ensure responsible application of the products of the technology while refraining from creating an environment which stifles research and development. Just as pharmaceuticals and chemicals are regulated for safety, it seems reasonable to require the products of genetic engineering to demonstrate lack of potential hazard. Uncertainty about possible Federal intervention is, however, not conducive to a flourishing of research and development. Some decisions need to be made, and soon.

Do you feel that the Federal agencies currently have the technical capability and resources to reach reasonable decisions and adequately consider benefits and risks?

My association with the subject of genetic engineering originated because of my interactions with the Environmental Protection Agency. At the time I did my study on introduced species for EPA, only a few knowledgeable and far-seeing individuals in the agency were concerned about these issues. Now, two years later, the concern has spread but knowledgeability has not necessarily kept pace. I understand that EPA has recently announced its intention to acquire more expertise in this area. This will be an essential step in preparing the agency to accept the role of regulating the products of genetic engineering. I am not as familiar with the technical capabilities of other agencies. I certainly support the intention of NIH to acquire ecological expertise on the RAC since this is currently the primary Federal decision-making body on recombinant DNA. Of course, it should be emphasized that no agency can be expected to have resources that haven't been developed yet. There are still so many unanswered questions.

Where, if anywhere, do gaps exist in our regulatory structure for approving and controlling release of genetically modified organisms into our environment?

The biggest genuine gap exists in the area of oversight of research and development. The Toxic Substances Control Act does not apply to R&D activities, and thus field testing of recombinant organisms is not covered. Although the NIH guidelines do cover R&D, technically these only apply to recipients of NIH funding. Compliance by the private sector is voluntary, and I do not believe this compliance should be counted upon indefinitely. Other defects in the NIH oversight process are related to the make-up of the RAC (although the lack of ecological expertise is in the process of being corrected) and the basic informality of the RAC review procedure. There is, as yet, no standardized method for evaluating requests for field testing and no established criteria for what information is needed to make a decision. As Mr. Karny's testimony emphasized, the RAC procedure clearly is in contrast to the major comprehensive review activities required for drug or pesticide approval. Since the hazards that organisms with recombinant DNA might pose to the environment are so poorly characterized as yet, this informality is perhaps insufficient for adequate decision making.

What are our options with respect to regulating the introduction of these organisms into the environment?

My perception is that, aside from leaving things just as they are, there are two major avenues which could be pursued. One is to amend TSCA to more definitively encompass the products of genetc engineering. The second is to make the NIH guidelines mandatory and formalize the RAC review procedure. Either way, there might still be problems. NIH is not a regulatory agency, and may decline the responsibility to enforce mandatory guidelines. And even amending TSCA to explicitly cover recombinant DNA would not solve the problem of lack of coverage for field testing. The third option is, of course, new legislation.

Do we need new legislation?

This is, of course, the bottom line, but it is also the question on which I am most reluctant to commit myself. The trouble with laws is that, once they are in place, it's hard to make them go away. And since we are not really sure what magnitude of risk we are dealing with, there is the distinct possibility that a legislative solution could create an overkill situation. Given these caveats, I think that some solution is definitely needed which will require a change in regulatory apparatus. Since it seems rather unlikely that either TSCA could be overhauled to close the gaps and still be a viable statute or that NIH will be willing to get into the business of regulating, maybe we do need something new. The something new ought, I think, to be constructed only as a temporary measure to fill the gaps until we learn more about what we are dealing with.

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JOHN H. GIBBONS
DIRECTOR

August 9, 1983

The Honorable Albert Gore, Jr.
Chairman
Subcommittee on Investigations
and Oversight
Committee on Science and Technology
U.S. House of Representatives
Washington, D.C. 20515

Dear Congressman Gore:

I am responding to your letter of July 25, 1983, that raises several questions in connection with the June 22 hearing on the release of genetically manipulated organisms into the environment. The questions and my responses are enclosed.

I should note that OTA is precluded from making the kinds of policy judgments that some of the questions request. However, I have endeavored to answer the questions completely and to provide policy analysis within the limits of this constraint.

If you have any further questions, please do not hesitate to get in touch with me at 6-2090.

Sincerely,

Geoffrey M. Karny

Geoffrey M. Karny

Enclosure

QUESTIONS AND RESPONSES

1. What should be the role of the Federal government in overseeing the introduction of organisms with new genotypes into the environment?

The Federal government's role necessarily will depend on the risk presented by the introduction of organisms with novel genotypes into the environment. Unfortunately, the precise nature and degree of the risk is unknown. Moreover, as Drs. Alexander and Sharples mentioned, it may be exceedingly difficult to develop a methodology to assess the risk. However, the EPA's Office of Pesticide Programs has developed criteria for testing biological pesticides, such as bacteria that kill certain insects, before approved for use by EPA. These criteria are concerned in part with the environmental impacts of biological pesticides, and they should provide important guidance in developing a similar set of criteria for evaluating the risks presented by the environmental use of genetically modified organisms. Moreover, past experience would lead us to believe that there probably is a risk from such novel organisms, although there are caveats about applying that experience to the case of genetically modified organisms.

In summary, there is major uncertainty about the risks, and there is reason, based on past experience, not to dismiss the risks as purely conjectural. Thus, a strong argument can be made that the Federal government should develop a method for assessing the risks and probably should act to assure that some form of risk assessment, even at its current crude level of development, be done for each case where release of a genetically modified organism into the environment is proposed. Of course, the degree of risk assessment will vary. There is less concern about genetically modifying most agriculturally important plants than about manipulating certain microorganisms with which scientists have had much less experience.

There are many possible mechanisms for how this oversight should be exercised. Currently, it is handled by NIH under the quasi-regulatory Guidelines for Research Involving Recombinant DNA Molecules. At the hearing, EPA asserted jurisdiction under the Toxic Substances Control Act (TSCA), which would mandate EPA review prior to the release of genetically modified organisms. Regardless of the form of oversight, most observers would agree that there should be Federal oversight, that it should be centralized or at least well-coordinated among different agencies, and that it should occur on a case-by-case basis before an organism is released.

2. Do you feel that the Federal agencies currently have the technical capability and resources to reach reasonable decisions and adequately consider benefits and risks?

As I mentioned above, risk assessment in this area is at a rudimentary level. Thus, one might argue that no one in or out of government currently has the capability to make reasonable decisions. There is a serious need for research to develop improved risk assessment methodology.

Setting aside this limitation, the Federal agencies probably have the capability to apply current knowledge to make these decisions. The NIH's Recombinant DNA Advisory Committee (RAC) certainly has expertise in the area of recombinant DNA (rDNA) technology. The RAC has no ecologists, but it can draw on the expertise of the USDA and EPA. USDA has significant expertise on plant and animal pests in its Animal and Plant Health Inspection Service (APHIS). EPA has expertise in the area of ecological impacts of organisms because of its experience with biological pesticides, but it has little, if any, expertise in the area of rDNA technology.

My major concerns are whether this expertise can be brought together in a focused, effective manner and whether there would be sufficient personnel and other resources if a large number of proposals involving deliberate release were submitted at once. Even with EPA taking the lead under TSCA, I would have concerns about the resources and expertise in its Office of Toxic Substances for the reasons I mentioned in my written statement. On the other hand, if the area of deliberate release develops slowly, as it seems that it will, and if EPA makes a concerted effort to develop its expertise in this area, then I would have much less concern.

3. Where, if anywhere, do gaps exist in our regulatory structure for approving and controlling releases of genetically modified organisms into our environment?

The existing regulatory structure is composed of the following: 1) the NIH Guidelines; 2) the Toxic Substances Control Act (TSCA); 3) several statutes covering plant and animal pests; and 4) tort law.

Each of these has important limitations in its applicability to deliberate release. Compliance with the Guidelines is voluntary unless an institution receives Federal funds for rDNA research, and there are other limitations in the RAC review procedure, which I detailed in my written statement. The USDA statutes are directed toward controlling the importation and interstate shipment of identified plant and animal pests. I question how easily they could be applied to deliberate release and whether APHIS has enough expertise in molecular biology to evaluate the risks. TSCA is the most flexible and broadly applicable statute, but there are some drawbacks to relying on it, which will be discussed in the answer to the next question. Tort law acts in a quasi-regulatory fashion because the possibility of large monetary damages provides incentive for safety, but it is designed primarily to compensate for injury after the fact. Clearly, it is useless as an oversight mechanism.

Whether or not this regulatory structure as a whole contains serious gaps depends on your philosophy of regulation. One could argue that the different elements overlap sufficiently so that there are no gaps. On the other hand, one could argue that this balkanized system creates a situation where the problem is likely to "fall through the cracks". Before EPA asserted jurisdiction under TSCA, it was my personal belief that there was a serious gap in this system. If EPA takes the lead by implementing a serious oversight program, then I would not see any gaps in the system. Whether or not the system is adequate to address any risks, however, is a different issue.

4. Do you agree with EPA that it has authority under TSCA to regulate deliberate releases?

I would have to answer this question with a qualified yes. A consensus has developed among the experts that TSCA probably covers genetically modified organisms. Living organisms are composed of chemical substances, which the statute covers. In addition and most importantly, Congress specifically designed and intended TSCA to fill in any gaps in other environmental laws. Moreover, TSCA clearly applies to rDNA molecules, and one could argue that the organisms can be regulated indirectly by regulating the rDNA molecules that they contain. Finally, EPA has applied TSCA to organisms in the past by listing certain bacteria and fungi on its inventory of existing chemical substances.

However, the matter is not free from doubt because credible arguments can be made that TSCA does not cover organisms. The legislative history--as far as I know--does not indicate that Congress specifically considered organisms when it developed the statute. Similarly, one could argue that the fair and ordinary meaning of the phrase "chemical substance" does not include organisms and, thus, Congress did not intend them to be covered. In addition, the definition of chemical substance in the statute refers to substances "of a particular molecular identity". While scientists may know the particular chemical make-up of parts of organisms, no one knows the complete chemical make-up of any living organism. (The definition of chemical substance does refer to substances occurring in nature, but I would not read that as the key part of the definition.) Finally, former EPA Administrator Douglas Costle provided a negative answer to this specific question in 1977. (For further information, see page 9 of my prepared statement.) While his statement is in no way determinative of the issue, it might be accorded some authority by a court.

5.& 6. Should TSCA be amended to clarify the jurisdictional issue? Do we need new legislation?

Judgments on legislation necessarily will depend on your view of the risks. If you believe that the risks are serious enough to warrant placing the burden of proving safety prior to release on those who would use genetically modified organisms in the environment, then new legislation would be necessary to accomplish that goal. TSCA could not be relied upon because it is a notification statute; the manufacturer of a new chemical substance is required to notify EPA of its intention to begin manufacturing the substance and to provide any data it may have on the substance's health or environmental effects. The burden is then on EPA to move forward. In some cases EPA may have to take legal action to get the data it believes it needs to evaluate the risk. Clearly, Congress believed that this would be sufficient for regulating new chemical substances. In contrast, Congress placed a higher burden on manufacturers of new drugs and pesticides because the governing statutes require the manufacturers to demonstrate safety before selling the product.

If you believe the risk to be modest or uncertain, TSCA would be a good regulatory tool because it is designed to collect information on chemical substances so that the risk can be evaluated. Amending TSCA to clarify its applicability to genetically modified organisms would be useful in order to remove uncertainty in the regulatory picture. Uncertainty can have a major effect on business planning and can result in socially useful projects not being undertaken. On the other hand, EPA has taken the position that TSCA applies, and in the absence of a challenge to this position by those affected, amending TSCA would probably not be necessary.

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August 12, 1983

Hon'ble Mr. Albert Gore, Jr.
Chairman
Subcommittee on Investigations and Oversight
Committee on Science & Technology
U.S. House of Representatives
Suite 2321 Rayburn House Office Bldg.
Washington, D.C. 20515

Dear Mr. Gore:

Thank you for your letter of July 25, 1983. I am enclosing written response to the questions you sent to me, and would be happy to respond to any other questions you may have in the future.

Thank you again for your kind invitation to testify.

Yours sincerely,

AM Chakrabarty

A.M. Chakrabarty, Ph.D
Professor of Microbiology

AMC:de

Encl.

Q. What do you see as the potential environment damage, if any, that could result from the release of new organisms such as the ones you are developing?

A. I do not really see any potential damage to the environment because of the use of laboratory-developed microorganisms. This is because these microorganisms are derived from nature, and have been changed in such a way that they could now 'eat' some toxic chemicals at an enhanced rate. No other genetic changes have been conferred on them. Thus the newly developed bacteria are no different from their natural parents in all other respects, and pose little additional danger to the environment.

Q. Do adequate safeguards exist to ensure that environmental damage will not result once these new organisms are released into the environment?

A. It is difficult to completely eliminate the possibility that application of laboratory-developed microorganisms will not cause any environmental problem. It is extremely unlikely, however, that they will, unless they have been modified to contain uncharacterized eukaryotic genes, whose products may have profound biological activity towards animals. After all, the initial concern for the recombinant DNA technology was due to introduction of eukaryotic genes in prokaryotes and vice versa, not due to genetic manipulation in bacteria per se. Scientists at various universities have been purifying bacteria from nature for years, studying and altering their genes, and throwing them back into the environment through the laboratory sink, and I do not know of any hazards coming out of such practice. The question of safeguards comes only when known pathogenic traits or uncharacterized eukaryotic genes are deliberately introduced into microorganisms for ultimate release into the environment.

Q. Is it possible that the microorganisms that you are developing will be the only feasible way to clean up places like Times Beach, Missouri? How do we use them safely and control their distribution?

A. For highly toxic chemicals that are distributed over a wide area at low to moderate concentrations (dioxins, PCBs etc), the conventional physico-chemical methods are either unsuitable or too expensive. That's why places like Love Canal, Seveso etc are fenced off and the highly contaminated soil and water are removed as much as possible for safe storage. Microorganisms traditionally have been responsible for recycling natural wastes, and they do so efficiently so that all the leaves or oily wastes are seldom found after a few months. It is the inability of natural microorganisms to degrade synthetic highly chlorinated compounds such as dioxins or PCBs, that has resulted in the toxic chemical pollution problem. My hope is that laboratory evolution of new genes for the degradation of such recalcitrant compounds will enable microorganisms to recycle such toxic wastes and convert them to innocuous metabolites. Thus I see microbial technology as the only feasible way that is inexpensive and ecologically acceptable. From our limited data on the survival of a 2,4,5-T degrading culture in soil, I think such laboratory-developed microorganisms tend to die off quickly after the toxic pollutant is gone, suggesting that their use does not pose any potential hazard. However, this has to be and can be conveniently checked for each and every microorganism designed for use in toxic waste dump sites.

Q. How specifically can we tailor bacteria for a particular application? What are the risks of a bacterium mutating into a more destructive form after its release?

A. Most enzymatic reactions are highly specific which means that bacteria can be tailor made for a limited number of specific functions. Since degradation of hydrocarbons or chlorinated compounds involves a series of specific steps, a tailor made bacterium for 2,4,5-T degradation seldom is altered in any other function. The risk of a bacterium mutating into a more destructive form is extremely low, since bacterial pathogenicity is usually a complex trait, that cannot be generated by single mutational processes. This concept has been reinforced repeatedly during the recombinant DNA controversy.

Q. Industry is not legally required to adhere to the NIH guidelines for recombinant DNA research, but it has done so voluntarily to date. As the field becomes more competitive, the need for secrecy will increase. Do you think that voluntary adherence will continue to work? Do we need legislation in this area to ensure that all firms play by the same rules?

A. In my opinion, the voluntary adherence has worked well so far and there is no reason to change it at this time. If, however, in the future it turns out that many industries are not complying with the guidelines, a need for legislation will certainly arise.

Q. Industry will most certainly develop gentically engineered microorganisms for the closed processing of materials. Some of these may represent a risk to the environment if accidentally released. How should we handle this possibility? Who specifies what testing should be done? Who should evaluate the risk to the environment? Who should have the final say on whether such an organism should be used and how?

A. Given the fact that various viral and animal genes including oncogenes are being cloned for vaccine preparation or simply for basic understanding of diseases such as cancer, and that such genes, when introduced into animal germ lines by microsurgery appear to be expressed functionally, it is imperative that appropriate precautionary measures be taken to avoid accidental release of such cloned genes into the environment. The NIH guidelines presumably address this problem. It would be highly desirable to have a second advisory committee, composed mainly of ecologists, environmental health engineers, microbiologists, geneticists, lawyers, and members of public having concern for the environment, not only to evaluate risks associated with massive accidental release of cloned eukaryotic genes into the environment, but also to formulate appropriate guidelines for the use of microorganisms designed to be used in an open environment. The committee should have access to all data pertaining to the pathogenicity and toxicology of the organisms, the nature of the genetic improvement, the extent of survival of the organisms in the open environment etc, so that it can make judicious decisions on the advisability of applying the microorganisms in an open environment, and defining the risk benefit ratios of such an application. This committee, in my opinion, should have the final say on whether such an organism should be used and how.

Q. How soon do you anticipate these genetically engineered organisms becoming commercially available?

A. I think some organisms ready for field trial will be constructed in about a year. The commercial application may take two to three years, depending upon the effectiveness of such cultures.

Q. What gaps in our knowledge about these organisms presently exist?

A. Each organism that would be constructed, particularly for application in an open environment for toxic chemical degradation, oil recovery etc, would be different. Enough information for such organisms, particularly for potential toxicity or virulence, must be obtained before their use should be permitted. Well defined guidelines promulgated by an advisory committee would be vital for safe handling, and application of such microorganisms.

Q. How should we weigh the relative potential risks presented by the release of these organisms against the potential benefits?

A. This is, of course, a subjective decision and can only be made when all the facts regarding the risks and benefits are at hand. Some people are too cautious and insist on nearly zero risk. Some people take a pragmatic view of an emerging technology and may be willing to give it a chance provided the benefits are real and the risks too little. In general, I favor limited inclusion in the advisory committee members of public who have been afflicted with the problems the technology is trying to solve, i.e., people from Times Beach or Love Canal who have lost their homes should have an equal opportunity to determine if microorganisms for dioxin or chlorophenol degradation should be used for toxic waste dump treatments; similarly, perhaps somebody suffering from cystic fibrosis, sickle cell anaemia or diabetes should also sit in a committee determining the potential application of gene therapy and the risk, benefit ratio of such therapy.

Q. What regulations or guidelines govern the research that you are now conducting?

A. Basically NIH guidelines.

Q. What guidelines or regulations would you have to comply with if you wanted to release these organisms into the environment?

A. Since my work involves little recombinant DNA technology, and no cloning of eukaryotic genes, as far as I am aware, there are no guidelines or regulations that I have to comply with.

Q. Do you see a need for a new or additional guidelines?

A. I do. I feel that NIH guidelines basically address the problems of accidental release of microorganisms harboring cloned eukaryotic genes or prokaryotic genes determining virulence, production of toxins or products of high biological value. It does not address the problems associated with the large scale use of microorganisms that have been genetically manipulated by in vivo genetic techniques or that may contain cloned genes that are exempt from NIH guidelines. Most of the microorganisms I expect to develop for use in toxic waste dump sites or for oil recovery and pollution clean up are being or will be constructed by natural gene manipulation techniques and therefore are exempt from NIH guidelines. Yet, I feel that it would be useful for me to approach an advisory committee with detailed data regarding the toxicity of these microorganisms, their potential in removing toxic or oily wastes from contaminated areas, and the nature of the problem that the microorganisms are designed to solve, so that a realistic appraisal could be made regarding the risks and benefits associated with the use of such microorganisms. Such appraisals can best be made through defined guidelines that do not exist at present.

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ESTABLISHED 1802

E. I. du Pont de Nemours & Company
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CENTRAL RESEARCH & DEVELOPMENT DEPARTMENT

September 8, 1983

Hon. Albert Gore, Jr.
Chairman
Subcommittee on Investigations and Oversight
Committee on Science and Technology
House of Representatives
Suite 2331 Rayburn House Office Building
Washington, D.C. 20515

Dear Mr. Gore:

This is in response to your letter of July 25, 1983 seeking answers to additional questions pertaining to the potential environmental impacts of deliberate releases of genetically engineered organisms that the Subcommittees were unable to ask at the June 22 hearing.

Answers to the additional questions are given on the attached sheets.

I welcomed the opportunity of participating in the hearing and trust that the answers submitted with this letter will prove helpful.

Sincerely,

Ralph W. F. Hardy
Director-Life Sciences

Attachment

RESPONSE TO QUESTIONS FORWARDED BY LETTER OF JULY 25, 1983 TO RALPH HARDY FROM CONGRESSMAN ALBERT GORE, JR., CHAIRMAN SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

Q. What do you see as the potential environmental damage, if any, that could result from the release of new organisms such as the ones you are developing?

A. The potential for environmental damage in the field of agriculture is believed to be small or negligible, particularly if a controlled, stepwise, progressive program of releasing new organisms into the environment is begun in the laboratory, moved with deliberate caution through the greenhouse, and then followed by closely supervised limited field evaluations. Man has been using new bacteria and has selected genetically superior plants for centuries to achieve desirable results. Specially grown bacteria useful in fermentation and hybrid plants used in agriculture are examples. Genetically engineered bacteria and plants are a logical extension of such practices.

Q. Do adequate safeguards exist to ensure that environmental damage will not result once these new organisms are released into the environment?

A. Yes, the revised NIH Guidelines for Research Involving Recombinant DNA Molecules, including its provision for Institutional Biosafety Committees (IBC), and the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health provide adequate safeguards. Additional regulatory controls may be provided by existing Federal legislation, e.g., the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA) administered by the Environmental Protection Agency (EPA).

Q. How specifically can we tailor bacteria for a particular application? What are the risks of a bacterium mutating into a more destructive form after its release?

A. It appears bacteria can be tailored, i.e., genetically engineered, very specifically for a particular application. This science is early in its development and there has been some apparent success with relatively simple molecules. More time and experience will be needed, however, to determine if genetic engineering on more complex systems is both feasible and practical.

The risks of a tailored bacterium mutating into a more destructive form after its release is small.

Q. Industry is not legally required to adhere to the NIH guidelines for recombinant DNA research, but it has done so voluntarily to date. As the field becomes more competitive, the need for secrecy will increase. Do you think that voluntary adherence will continue to work? Do we need legislation in this area to ensure that all firms play by the same rules?

A. Yes, we believe voluntary adherence will continue to work. In our experience, firms involved in this area have recognized the need to follow the guidelines from both a safety and product liability standpoint and we expect that they will continue to do so. We believe existing legislation such as FIFRA, TSCA and the Food, Drug & Cosmetic Act (FDC) provide adequate jurisdiction for agencies with expertise in regulating new developments to oversee activities in biotechnology. In addition, the scientific community has established guidelines to be followed. Thus, we see no need for additional legislation at this time.

Q. Industry will most certainly develop genetically engineered microorganisms for the closed processing of materials. Some of these may represent a risk to the environment if accidentally released. How should we handle this possibility? Who specifies what testing should be done? Who should evaluate the risk to the environment? Who should have the final say on whether such an organism should be used and how?

A. As indicated above, existing Federal agencies under present law will monitor the introduction of new materials whether they be created by traditional chemical technology or biotechnology. As part of this approval system, the agencies would assure that the materials can be made and used safely. With regard to evaluation of risk, we believe it is the obligation of both the manufacturers and the Federal agencies to assess the risk and assure the public that the new material can be made and used safely. For example, my company has a policy that it will not manufacture a product unless such product can be made, used, handled and disposed of safely.

Q. How soon do you anticipate these genetically engineered organisms becoming commercially available?

A. Products produced utilizing genetically engineered organisms have already been developed for commercialization, for example, insulin has been approved by the FDA for sale. The growth in this area of commerce is expected to expand rapidly throughout the coming decade.

Q. What gaps in our knowledge about these organisms presently exist?

A. Since biology is not an exact science and evolution is an ongoing process, there will always be gaps in our knowledge of living organisms. However, with the current state of knowledge and understanding of genetic engineering, we believe that biotechnologists foresee little probability of harm to human health or the environment from implementation of this technology.

Q. How should we weigh the relative potential risks presented by the release of these organisms against the potential benefits?

A. There has been no credible evidence published to date showing actual risk presented by the release of genetically engineered organisms. On the other hand, substantial benefit from use of such organisms has yet to be proven. Thus, the question of assessing the risk/benefit ratio is premature and not answerable in any nonsubjective way.

Q. What regulations or guidelines govern the research that you are now conducting?

A. Besides our own corporate policy as stated above, the NIH Recombinant DNA Guidelines, RAC's recommendations and local Institutional Biosafety Committees, as well as local ordinances and tort law in general, govern the recombinant DNA research now underway at Du Pont. Recent press reports indicate that in the foreseeable future, regulation of products of biotechnology as they begin to meet the marketplace will fall under the Environmental Protection Agency.

Q. What guidelines or regulations would you have to comply with if you wanted to release these organisms into the environment?

A. We do comply with the NIH guidelines and as stated above, believe that commercial manufacture of such materials for release into the environment would subject the manufacturer to the jurisdiction of the Federal laws mentioned above.

Q. Do you see a need for new or additional guidelines?

A. No need is currently seen for new or additional guidelines.

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The Honorable Albert Gore, Jr.
Chairman, Subcommittee on
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Committee on Science and Technology
House of Representatives
Washington, D.C. 20515

Dear Mr. Gore:

In reply to your letter of July 25, as a follow-up to the June 22 hearings, I am enclosing responses to your questions. I also enclose a list of the members of the NIH Recombinant DNA Advisory Committee (RAC), and a list of members of RAC Plant Working Group.

Sincerely,

Bernard Talbot

Bernard Talbot, M.D., Ph.D.
Deputy Director
National Institute of Allergy
and Infectious Diseases

Enclosures

Responses of Dr. Bernard Talbot

Question: What mechanisms currently exist for coordination of Federal oversight activities of deliberate releases? The RAC is the body with the most extensive experience with questions of genetic engineering. How does the RAC interact with the other Federal agencies?

Answer: Other Federal agencies have non-voting representatives to the NIH Recombinant DNA Advisory Committee (RAC). Footnote two to my written testimony lists these representatives. They participate actively at the RAC meetings. Also, in each of the three cases of deliberate release to the environment which have been approved by NIH to date, subsequent to the RAC recommendation for approval, but prior to NIH final approval, advice was sought from the Department of Agriculture Recombinant DNA Committee. This Committee contains members not only from USDA, but also from NIH and the National Science Foundation. Between 1976 and 1980, eleven meetings were held of the Federal Interagency Advisory Committee on Recombinant DNA Research, in addition to a number of meetings of its subcommittees.

Question: Do we need to legislate a transition point between RAC oversight and oversight by other Federal agencies?

Answer: The interaction between other Federal agencies and the RAC is excellent. I do not believe legislation is necessary.

Question: How should we balance the potential risks and benefits involved with deliberate releases?

Answer: In the consideration by the RAC and by the Department of Agriculture Recombinant DNA Committee of individual cases of proposed releases, the potential risks and benefits are considered and discussed prior to the vote on whether or not to recommend approval.

Question: It appears that USDA has very limited authority to regulate the introduction of new or modified organisms resulting from genetic engineering. Is that perception correct? Should the USDA have greater authority?

Answer: I have no detailed knowledge of USDA's authorities and consequently have no opinion as to whether they should have greater authority.

Question: There is a long history of a man modifying plants and animals by classical breeding methods. How is altering organisms by genetic technologies different from past practices? Do we need to treat organisms developed by recombinant DNA methods differently for purposes of regulation?

Answer: Modern genetic techniques give man the possibility to modify plants and animals more precisely and more quickly than previously possible. Organisms not developed by recombinant DNA methods would not fall under the NIH Guidelines for Research Involving Recombinant DNA Molecules. Organisms developed by recombinant DNA methods would fall under the Guidelines (unless they were in a class defined in the Guidelines as exempt from the Guidelines).

Question: What do you see as the potential environmental dangers, if any, posed by the introduction of new genetically engineered organisms into the environment?

Answer: I agree with Dr. Martin Alexander's statement that, "alien organisms that are inadvertantly or deliberately introduced into natural environments may survive, they may grow, they may find a susceptible host or other environment, and they may do harm. I believe that the probability of all these events occurring is small . . . ."

Question: What is your opinion of EPA's decision to assert jurisdiction under TSCA over deliberate releases?

Answer: I have no detailed knowledge of TSCA nor EPA's authorities and consequently have no opinion on this issue.

Question: Industry is likely to develop genetically engineered microorganisms for use as biocatalysts in closed systems. Some might pose a risk to the environment if released accidentally. Given that the RAC's jurisdiction is limited to research supported by Federal funding, could the RAC control the development and use of these microorganisms?

Answer: Footnote 11 to my written testimony lists those localities which mandate compliance with the NIH Guidelines. For work not taking place in one of these localities, and not supported by Federal funds, compliance with the NIH Guidelines is voluntary. Industry has voluntarily submitted many proposals to the NIH for RAC review.

Question: The RAC has created a Working Group on Plants and Associated Microorganisms to approve field trials of genetically engineered plants. It is our understanding that this Working Group will review proposals in secrecy. We realize that industry has a need to protect its proprietary information. However, one of the reasons for the public confidence in our current procedures for handling genetic engineering research has been the openness of the procedure for evaluating research proposals. How do we reconcile these two conflicting needs?

Answer: The RAC Plant Working Group and the full RAC will review proposals in closed session when the submissions involve material designated by the submitter as confidential, proprietary information. The RAC went into closed session for such reviews at its meetings in September and December 1979, March, June and September 1980, and January, April and September

1981. Following these parts of the RAC meetings closed to the public, whenever the NIH approved an action which had been recommended by the RAC in closed session, an announcement was placed in the Federal Register giving notice of this action to the public. (The first such notice appeared as "Additional Announcement of the Director, NIH," Federal Register, Volume 44, Number 232, page 69251, November 30, 1979.) Such a Federal Register notice is a way of reconciling the need to protect the detailed proprietary information submitted for review, and yet inform the public of the NIH action on the submission.

Question: When revising its guidelines recently the RAC initially proposed to leave approval of plant field tests entirely up to local Institutional Biosafety Committees. Could you explain the rationale for this initial proposal? Do you believe that the Federal government has a role to play in overseeing the technology?

Answer: It is not correct that "the RAC initially proposed to leave approval of plant field tests entirely up to local Institutional Biosafety Committees." The statement is wrong in two ways. The suggested Guideline revision was submitted for RAC consideration, not proposed by the RAC; and the suggested revision would not have left approval of all plant field tests entirely up to local Institutional Biosafety Committees (IBCs) but rather only those plant field tests which met certain defined criteria. The proposal was discussed at the April 11, 1983, RAC meeting, at which time the RAC made several modifications in the specific criteria which the experiments must meet to fall into this class. They also modified the approval procedure to require not only IBC approval, but also approval by a Plant Working Group of the RAC. They then voted to recommend this change in the Guidelines. The change was subsequently endorsed by the Department of Agriculture Recombinant DNA Committee. It was subsequently accepted by NIH (Federal Register, Volume 48, No. 106, page 24548, June 1, 1983) and now appears as Appendix L to the Guidelines. I believe the current Guidelines define an appropriate role for RAC and NIH in overseeing the technology.

Question: One concern that has been voiced about regulation in this area is that it might stifle development of the technology. Do you think this is a realistic fear?

Answer: I believe that the NIH Guidelines provide oversight of safety of recombinant DNA experiments without stifling development of the techology.

Question: What would be the probable consequence if no efforts at regulation were made? Could industry police itself with regard to ensuring that releases occur under environmentally safe conditions?

Answer: We have no evidence of any industrial non-compliance with the NIH Guidelines. Certain localities mandate compliance with the NIH Guidelines. Throughout the rest of the country, to the best of our knowledge, all industrial concerns are in voluntary compliance with the NIH Guidelines.

Question: What steps do you see the RAC taking in the future to oversee deliberate releases of new genetically engineered organisms?

Answer: Under the current NIH Guidelines, deliberate release of certain plants meeting the criteria detailed in Appendix L to the Guidelines, can be approved by NIH following review by the RAC Plant Working Group. I expect there to be a number of such submissions in the future to the RAC Plant Working Group for their review. Under the current NIH Guidelines, deliberate release not meeting the criteria detailed in Appendix L can be approved by NIH only after review by the full RAC. I expect there to be a number of such submissions in the future to the full RAC for their review.

Question: Do you foresee an eventual relaxation or additional modification of the NIH's general prohibition against deliberate releases?

Answer: The NIH Guidelines have been modified many times since their original promulgation in 1976. At essentially every RAC meeting, proposals for changes in the Guidelines have been discussed and voted upon; and NIH has usually subsequently accepted the recommended changes and modified the Guidelines. Therefore, it is to be expected that in the future there will be further changes in the Guidelines.

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Honorable Albert Gore, Jr.
Chairman, Subcommittee on Investigations and Oversight
Room 822, House Annex #1
Committee on Science and Technology
House of Representatives
Washington, D.C.   20515

Dear Mr. Chairman:

As you requested in your letter of July 25, we have prepared answers (enclosed) to the Subcommittees' questions pertaining to the potential environmental impact of deliberate releases of genetically altered organisms.

I apologize for the delay in answering these questions, and hope that this will not affect the inclusion of these points in the hearing record.

Thank you again for the opportunity to participate in the June 22 hearing.

Sincerely yours,

Don R. Clay

Don R. Clay
Acting Assistant Administrator
for Pesticides
and Toxic Substances

Enclosure

RESPONSES TO SUBCOMMITTEE QUESTIONS:

Q: What mechanisms currently exist for coordination of Federal oversight activities of deliberate release?

A: The National Institutes of Health Recombinant DNA Advisory Committee (RAC) is currently overseeing deliberate release of recombinant organisms when it is for research purposes, such as field testing. EPA's Office of Pesticide Programs (OPP) oversees deliberate releases for both experimental and commercial pesticidal uses, and the Food and Drug Administration (FDA) regulates pharmaceutical uses of biotechnology (although the latter are not likely to involve deliberate releases). At some point in the near future, we expect that deliberate releases for purposes other than those covered by OPP and FDA will begin; this is where the Office of Toxic Substances' (OTS') responsibility lies. OTS plans to work closely with the RAC, OPP, FDA, and other agencies with biotechnology responsibilities to clarify the points at which our responsibilities may overlap. Understandings between OTS and these other groups and agencies will probably be reached in the next year or so. We will also be discussing with these other agencies whether or not it would be beneficial to reinstate an inter-agency workgroup on biotechnology. While these plans are under consideration, coordination is continually assured through the RAC, which has representatives from all of the federal agencies of concern.

Q: The RAC is the body with the most extensive experience with questions of genetic engineering. How does the RAC interact with the EPA in assessing the environmental impacts of deliberate releases?

A: As explained above, EPA has a representative on the RAC, and it will be working with the RAC to ensure a coordinated approach to safety assessment of genetic engineering. We hope to draw on the RAC's experts as we develop significant policies and risk assessment strategies, and when we take action on specific chemicals and pesticides. We also hope to reciprocate by making the expertise within EPA freely available to the RAC as ecological questions and problems come to them. The RAC has also taken a step towards acknowledging the significance of environmental concerns associated with genetic engineering by their recent appointment of an ecologist to the committee.

Q: Do we need to legislate a transition point between RAC oversight and oversight by other federal agencies?

A: We believe that the transition point between RAC oversight and oversight by EPA and other federal authorities is generally clear and that further legislation is not necessary. As elaborated above, potential overlaps between legislative authorities can be handled by cooperation and perhaps by memoranda of understanding or other written understandings between the agencies in question.

Q: How should we balance the potential risks and benefits involved with deliberate releases?

A: The Toxic Substances Control Act (TSCA) provides a good model for balancing risks and benefits. Under this act, EPA has the authority to regulate "unreasonable risks." In determining whether a chemical presents unreasonable risks, EPA balances the probability that the substance will cause harm and the magnitude and severity of that harm against the adverse effects of Agency regulation of that chemical. These adverse effects would include loss to society of the benefits of the chemical (taking into consideration available substitutes), national economic consequences, and impacts on technological innovation. One of the major purposes of TSCA is to ensure that sufficient health and environmental effects data are developed on chemical substances to allow such an understanding.

Q: There is a long history of man modifying plants and animals by classical breeding methods. How is altering organisms by genetic technologies different from past practices? Do we need to treat organisms developed by recombinant DNA methods differently for purposes of regulation?

A: Genetic technologies for the first time allow the recombination of genes from organisms that could not or would not recombine in nature; this leads to the development of novel organisms. A number of theoretical risks associated with these organisms have been proposed by expert scientists. These concerns have been acknowledged and addressed not only by EPA, but also at the international level by committees of the World Health Organization and the Organization for Economic Cooperation and Development. Draft statements from both of these committees have recommended that careful assessment of potential risks be made. Nonetheless, no risks have been proven or disproven to date. The only way to determine whether organisms developed by recombinant DNA methods present new or different risks which might warrant epecial regulatory attention will be to test them in scientific studies using proper controls. EPA is planning to encourage such research in three ways: (1) by funding studies of the possible generic risks of recombinant DNA and other forms of altered DNA (mutants, for example), (2) by developing methodologies for testing the organisms to determine their potential hazards, and (3) by requesting data from companies which propose to use genetically engineered organisms in the open environment. Until a reasonable base of knowledge can be developed, EPA believes it is prudent and appropriate that products be tested for potential risks (e.g., under authority of section 5) before they are released into the general environment. Such testing could take place, for example, in contained or simulated natural environments.

Q: What do you see as the potential environmental dangers, if any, posed by the introduction of new genetically engineered organisms into the environment?

A: The potential dangers which experts have proposed are largely theoretical at this time, but include:

- o Ecological disruption due to lack of natural enemies in the environment.
- o Infectivity, pathogenicity, or toxicity to nontarget organisms (plants, animals, humans).
- o Exchange of genetic material with other organisms in the environment, infecting these organisms or disrupting ecosystems.

It is important to stress that these risks have neither been proven nor disproven in the case of genetically engineered organisms. However, we have experienced problems in the past when novel (non-engineered) organisms have been introduced into new environments. For example, significant economic and ecological disruption have been caused by gypsy moths, kudzu weed, and the chestnut blight. Because of the large amount of uncertainty and the potential magnitude associated with these risks, EPA believes that it is appropriate to take a cautious approach in the release of genetically engineered microorganisms into the environment.

Q: In a memorandum dated March 14, 1983, EPA counsel Stanley Abramson makes the point to Dr. John Todhunter that, although recombinant DNA and new life forms theoretically fit the definition of "chemical substances" for purposes of regulation under the Toxic Substances Control Act, commonly accepted scientific definitions would not include life forms as chemical substances. He also notes that there is no indication in the statute or in its legislative history that Congress intended TSCA to regulate life forms. In view of this, do you believe that EPA has the authority to regulate deliberate releases of genetically engineered life forms? Do we need additional legislation?

A: Although commonly accepted scientific definitions do not include life forms as chemical substances, and the TSCA legislative history does not address the potential applicability of TSCA to life forms, EPA believes that TSCA gives it the authority to regulate genetically engineered life forms. As described in the testimony I provided to the Subcommittees, we base this conclusion on the statutory definition of chemical substances and on the legislative history, which shows that TSCA was intended to be a "gap-filler." Genetically engineered organisms appear to fit within the legislative intent that TSCA should be used to address issues not adequately or effectively covered by other health and environmental laws. For these reasons, we do not believe that, at this point, we need additional legislation or an amendment to TSCA to regulate deliberate releases of genetically engineered life forms.

Q: Should TSCA be amended to clarify this jurisdictional issue?

A: For the reasons stated above, no.

Q: How soon do you foresee movement by EPA to attempt regulation of biotechnology under TSCA?

A: EPA has already taken some steps to develop an approach to biotechnology, the details of which may be found in my testimony. We anticipate that this program will be developing over the next few years, but the precise rate of development will depend on (1) budget and resource allocations, (2) how quickly we can rectify the current lack of scientific knowledge about potential risks, and (3) the pace at which products are commercialized, which will influence our knowledge about their potential risks and benefits and will determine the rate of premanufacture notice submissions under section 5 of TSCA.

Q: Industry is likely to develop genetically engineered microorganisms for use as biocatalysts in closed systems. Some might pose a risk to the environment if released accidentally. Under what authority would EPA control the development and use of these microorganisms?

A: Sections 5 and 6 of the Toxic Substances Control Act (TSCA) grant the Administrator of EPA authority to protect against risks associated with the "manufacture, processing, distribution in commerce, use, or disposal" of chemical substances. Thus, if a microorganism is being used as a biocatalyst for the manufacture or processing of a chemical, and if its accidental release would pose potential risks, it could be regulated under the authority of TSCA section 5 or 6 (depending on whether the chemical being produced was new or existing).

Q: One concern that has been voiced about regulation in this area is that it might stifle development of the technology. Do you think this is a realistic fear?

A: Federal oversight of any kind impedes technological developments to some extent, but there is no reason to believe that regulation under TSCA will stifle development of the biotechnology industry. Before EPA can regulate a product under TSCA, a finding that there may be an "unreasonable risk" or "substantial exposure" must be made. Of course, where that finding is made, the responsibility for alleviating these concerns falls on the manufacturers and producers of chemical products. However, EPA will take every reasonable step to minimize the negative impact of any regulation on innovation without compromising the aim of TSCA, which is to protect the human health and the environment from unreasonable risks.

Q: What would be the probable consequence if no efforts at regulation were made? Could industry police itself with regard to ensuring that releases occur under environmentally safe conditions?

A: In the short run, the biotechnology industry has been quite successful at policing itself and has been voluntarily complying with the guidelines established by the NIH Recombinant DNA Advisory Committee. In the long run, however, the intensely competitive nature of the biotechnology industry will presumably create strong incentives for companies to reduce their costs, including those associated with developing strong safety programs. Many companies might establish outstanding safety programs even without federal oversight, but we cannot reasonably expect that economically vulnerable companies will voluntarily place safety as a high priority when their economic success may be at stake.

Q: What obstacles -- both legal and scientific -- do you see to EPA's effort to regulate deliberate releases under TSCA?

A: At this point, scientific obstacles appear to be the most serious impediments to EPA's efforts. One issue which illustrates this, and having both scientific and legal components, is how and whether EPA should differentiate very similar but different organisms. For example, EPA must decide whether DNA which has had one gene replaced or altered is a "new chemical." This issue can be resolved through policy decisions, but the scientific significance of such minute differences will be difficult to determine. Also, as was mentioned in my testimony and in answers to several previous questions, very little testing for safety of recombinant DNA organisms has yet been done. Arguments that recombinant organisms are safe are usually based on the fact that we know of "no problems to date"; arguments that recombinant organisms may be dangerous are based on equally unscientific premises. In some cases, even the methods to test for risks have not been developed. Until this situation is rectified, it will be difficult for EPA to establish whether any specific product is either hazardous or safe. However, we are placing high priority on resolving these scientific issues as quickly as possible. In the meantime, we will combine EPA's knowledge of environmental sciences with the scientific expertise of the RAC, other federal agencies, industry, and academia, to establish reasonable case-by-case guidelines for hazard and safety assessment.

DEPARTMENT OF AGRICULTURE
OFFICE OF THE SECRETARY
WASHINGTON, D. C. 20250

Honorable Albert Gore, Jr.
Chairman, Subcommittee on
Investigations and Oversight
Committee on Science and Technology
U. S. House of Representatives
Washington, D. C. 20515

Dear Mr. Chairman:

This responds to your request of July 25, 1983, transmitting additional questions to complete your hearing record of the June 22 hearing on the potential environmental impacts of deliberate releases. Dr. Edgar Kendrick represented the Department at those hearings.

Enclosed are the questions and answers. We appreciate the interest of the Subcommittee in our research programs. We will be happy to provide any further information requested.

Sincerely,

Michael Hobach
for
ORVILLE G. BENTLEY
Assistant Secretary
for Science and Education

Enclosures

QUESTIONS AND RESPONSES
For Dr. E. L. Kendrick

What mechanisms currently exist for coordination of Federal oversight activities of deliberate releases?

> The mechanisms that exist for coordination of federal oversight activities of deliberate releases are not fundamentally different than those for other biologics, with one notable exception; i.e., such proposals are reviewed by the Recombinant DNA Advisory Committee (RAC) and, if they involve agriculture, by the USDA Recombinant DNA Advisory Committee (A-RAC).

RAC is the body with the most extensive experience with questions of genetic engineering. How does RAC interact with USDA in assessing the environmental impacts of deliberate releases?

> RAC interacts with USDA in having a scientist from USDA responsible to RAC for agricultural matters, in having some members of RAC drawn from the agricultural science community, and in having one or more members of RAC on A-RAC. In addition both RAC and A-RAC convene panels of scientists to review applications for release. Applicants are required to provide specific data relating to release, and upon release data concerning the organism/s are collected and reviewed by RAC or a designated working group.

Do we need to legislate a transition point between RAC oversight and oversight by other Federal agencies?

> Existing legislation and administrative authorities in practice for several years now suggest that currently and in the near future there is not a need to legislate a transition point between RAC oversight and that by other federal agencies. Insofar as agricultural and natural resource interests are concerned, existing legislation involving biologics/chemicals, their preparation and use is currently applicable and administered under existing authorities.

How should we balance the potential risks and benefits involved with deliberate releases?

> When the requirements for deliberate release are met, the questions of potential risks and benefits are not different from those now considered with existing mechanisms concerned with the balance of risks and benefits. The planting of native, American chestnut trees, or parts thereof that would provide such plants that had been approved for release by RAC and contained genetic information that imparted resistance to chestnut blight, would not impose a set of risk/benefit questions that in context are different from those raised prior to 1973. There would need to be updating of environmental and other socio/economic considerations in the same manner that would be necessary for American chestnut trees not requiring approval by RAC for release.

It appears that USDA has very limited authority to regulate the introduction of new or modified organisms resulting from genetic engineering. Is that perception correct? Should the USDA have greater authority?

> The perception that the USDA has very limited authority to regulate the introduction of new or modified organisms resulting from genetic engineering is correct. There should not be a perception that this limited authority is not adequate at this time. Greater authority is not perceived to be needed at this time.

There is a long history of man modifying plants and animals by classical breeding methods. How is altering organisms by genetic technologies different from past practices? Do we need to treat organisms developed by recombinant DNA methods differently for purposes of regulation?

> Altering organisms by genetic technologies is different from past practices in that entirely new techniques with massive potentials for changes in plants, animals, and microorganisms are now available world wide. The potential of these techniques to provide highly specific and entirely new combinations of genetic information for living organisms is a sharp departure from past practices. In addition to these remarkable changes of scope and scale, the potential for substantial reduction in time required for changes presents a departure from past practices. These changes do not suggest at this time that we need to treat such organisms developed by recombinant DNA methods inherently differently for purposes of regulation. However, we do perceive that existing authority and administrative practices may need to be exercised, for example to respond to certain epidemiological needs in agriculture wherein large acreages are involved. Other needs are also envisioned, but at this time do not require different treatment for purposes of regulation.

What do you see as the potential environmental dangers, if any, posed by the introduction of new genetically engineered organisms into the environment?

> No unique potential environmental dangers are envisioned by the introduction of new genetically engineered organisms into the environment of the nation by private and/or public interests in the United States, as long as existing oversight procedures are fully utilized. Specialized tracking systems for recognizing potential environmental dangers are being developed in agriculture to meet its unique needs, but again these are being developed under existing legislative authority.

What is your opinion of EPA's decision to assert jurisdiction under TSCA over deliberate releases?

> In our opinion EPA's decision to assert juridiction under TSCA over deliberate releases will not be harmful to the interests of the agriculture, forestry, and natural resources community and their private and public interests, providing there is not an assertion of claimed uniqueness for recombinant DNA derived plants, animals, biologics and/or chemicals and/or processes.

One concern that has been voiced about regulation in this area is that it might stifle development of the technology. Do you think this is a realistic fear?

> We believe the fear that regulation might stifle development of the technology is well founded, based primarily on experience. This is most especially critical in this area of high technology because of its complexity, its total availability world wide, and our struggle in this nation to provide an advanced level of technology transfer for application by our industries.

What would be the probable consequence if no efforts at regulation were made? Could industry police itself with regard to ensuring that releases occur under environmentally safe conditions?

> If *existing* efforts at regulation and oversight were not made the probable consequence would no doubt be confusion, conflict and possibly some human and environmental dangers. If industry did not adhere to *existing* regulation, with modifications as needed, and was not subject to existing oversight, with modifications as needed, (as they have demonstrated a willingness and desire to do), it would not be *perceived* that it could police itself in a manner that would protect either public or private interests satisfactorily.

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